

# Recurrent schizophrenia-like psychosis as first manifestation of epilepsy: a diagnostic challenge in neuropsychiatry

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**Abstract:** Since the 1950s, several studies have been carried out to investigate the occurrence of schizophrenia-like psychoses in epilepsy. The psychopathological profile comprises symptoms from the affective, schizophrenic, and cognitive domains and the prevalence varies between 2% to 20%. Classification of such conditions is performed according to their temporal relationship with the seizure itself. Although it is well known that epilepsy may be associated with psychotic disorders, it is less widely recognized that relapsing psychotic phenomena may be the first and only symptom of epilepsy. In this research, two patients are described who were initially referred for recurrent episodes of bipolar affective disorder and schizophrenic psychosis, respectively. In both patients, a diagnosis of relapsing postictal psychotic states due to previously undiagnosed epilepsy was made and consequently, treatment with antiepileptics was started. During follow up over several months, they remained free of both epileptic and psychotic symptoms. Given the kaleidoscopic nature of the postictal psychosis and full recovery from this, such psychoses best meet the criteria for a cycloid psychosis. These observations illustrate diagnostic and therapeutic pitfalls due to the conceptual disintegration emerging from the inadequate separation between psychiatry and neurology. Therefore, the importance of a neuropsychiatric viewpoint should be promoted.

**Keywords:** postictal psychosis, epilepsy, classification, cycloid psychosis, neuropsychiatry

By the middle of the 19th century, neuropsychiatrists from France and Germany, notably Morel and Magnan, and Griesinger and Kraepelin, respectively, had identified a recurrent association between epilepsy and psychosis. Based on the clinical affiliation, these psychoses were viewed either as an epileptic phenomenon or as part of the schizophrenic spectrum. Until the 1950s, the neurological vantage point dominated,<sup>1</sup> but following this time psychiatric aspects of epilepsy were rediscovered, resulting in an increase in the number of studies on schizophrenia-like psychosis in patients with epilepsy.<sup>2,3</sup> Psychoses in epilepsy, that may occur either peri- or interictally, are mainly characterized by symptoms from the affective, schizophrenic, and cognitive domains such as mood instability, anxiety, hallucinations and delusions, and confusion.<sup>4-7</sup> The prevalence varies from 2% to 7% but in temporal lobe epilepsy a percentage of nearly 20% is reported.<sup>8,9</sup> Furthermore, the incidence is higher in patients with a psychiatric history or longstanding epileptic manifestations.<sup>10-12</sup> The main differential diagnosis is a nonconvulsive or partial complex status epilepticus.<sup>13,14</sup>

Although the Subcommittee on Classification of the Commission on Psychobiology of Epilepsy of the International League Against Epilepsy

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(ILAE; <http://www.ilae-epilepsy.org>) has proposed a classification of neuropsychiatric disorders in epilepsy, an internationally accepted consensus on the classification of psychotic syndromes associated with epilepsy is still lacking.<sup>15,16</sup> Therefore, these conditions are generally classified according to their temporal relationship to the seizure itself, ie, ictal, postictal, and interictal psychosis.<sup>16,17</sup> Ictal psychosis is commonly associated with a partial complex status, lasts for hours to days, and is characterized by impaired consciousness. Interictal psychosis is not directly related to the ictus, can be either brief or chronic, and its characteristics are auditory hallucinations, paranoid delusions, and affective symptoms, or a purely delusional state. Chronic forms closely resemble schizophrenia. The most common form is the postictal psychosis that may persist for days or weeks. Mostly, a characteristic lucid interval is present that can last from 1 to 6 days between the epileptic seizure and the onset of psychosis. The psychotic symptoms are pleomorphic (delusions, hallucinations, catatonia) and frequently include confusion. Affective symptoms are often prominent and bizarre and disorganized behaviors occur regularly. The episodes resolve spontaneously but often recur, generally with a similar clinical picture.<sup>8,13,17</sup> In some patients, suppression of seizures may provoke psychotic symptoms and/or uninhibited behaviors. This condition was originally described by Landolt in 1953 who introduced the term alternative psychosis, later described as forced normalization, and that implies a tradeoff between seizure control and psychotic symptom occurrence.<sup>5,7,16</sup>

In this report, two female patients are described who were referred for evaluation for recurrent manic and schizophrenia-like symptoms, respectively, that were diagnosed as postictal psychotic states.

## Clinical observations and results

Patient A is a 41-year-old female who was admitted for the first time to the department of neuropsychiatry three years before because of disorganized behavior with motor agitation and euphoric mood that was preceded by a short period with psychiatric symptoms, especially paranoid ideation, ideas of reference, mood instability, inactivity, and self neglect. Psychiatric examination at admission showed a pleomorphic psychopathological picture characterized by anxiety, perplexity, impaired attention and distractibility, elation, instability of mood, flight of ideas, associative and incoherent thinking, psychomotor agitation, odd and chaotic behaviors suggestive of auditory hallucinatory experiences, and paranoid ideation. She was disorientated in time and place, had no insight, and experienced severe sleep disturbances. Psychi-

atric, neurological, or somatic antecedents were not present, nor was there a family history of neuropsychiatric disorders. A provisional diagnosis of subacute confusional state was made (ICD-10: F05.8). Extensive neurological, somatic, and laboratory examination, including analysis of cerebrospinal fluid and magnetic resonance imaging (MRI) of the brain, revealed no abnormalities. The patient was treated with a low dose of haloperidol (3 mg daily) and lorazepam (4 mg daily) after which the psychiatric symptoms gradually disappeared. Three months later she was discharged, at which time treatment comprised 3 mg haloperidol per day only.

During follow up over a period of one year, she developed symptoms of major depression with loss of interest, inactivity, anhedonia, suicidal ideation, flattening of affect, and depressed mood. Neuropsychological assessment revealed a total IQ of 86 with a harmonic profile and motivational problems. Haloperidol was discontinued and the patient was treated with imipramine under control of the plasma concentration. Lithium was later added as an additional treatment.

Because of persistent apathetic behavior, she was readmitted and all psychotropic drugs were discontinued. Subsequently, she developed psychotic symptoms, similar to those during the first admission and a provisional diagnosis of bipolar affective disorder was made. The patient was treated with a low dose of haloperidol, lithium, and valproic acid. She then collapsed twice resulting in severe facial lacerations. The collapses were followed by a short period of confusion, bizarre behavior, and perplexity. A complete reevaluation of her medical history was made from which it appeared that there had been two synopes at the age of 19 years and, most probably, an astatic seizure prior to her first hospitalization. The collapses in her recent history were reconsidered as tonic-clonic seizures, which was corroborated by a 24-hour electroencephalography (EEG) recording showing bilateral frontotemporal sharp wave activity (left more pronounced than right). Subsequent EEG recording during sleep disclosed mid frontopolar epileptic activity. A definite diagnosis of cycloid psychosis (ICD-10: F23.0) related to epilepsy, more specifically postictal psychosis, was made. An MRI of the brain (1½ Tesla) demonstrated that, apart from a slightly, but discrete, dilated left temporal horn, there were no abnormalities present. Psychotropics were tapered off but valproic acid was continued. In the following months, periods of unstable mood and distractibility remained without clinical signs of epilepsy. Carbamazepine was therefore added, however, its use was discontinued due to an allergic skin reaction, at which point it was replaced by oxcarbazepine. During follow up over more than 6 months, the patient used 900 mg of

valproic acid in combination with 300 mg of oxcarbazepine (plasma concentrations 75 mg/L and 4.4 mg/L, respectively). There was no further occurrence of epileptic or psychotic phenomena, or disturbances in mood stability.

Patient B is a 16-year-old female who was referred for reevaluation of short lasting (3 days to 2 weeks) recurrent psychoses with full recovery since her menarche at the age of 13. The psychotic episodes were characterized by mood instability, suicidal ideation, pananxiety, confusion, auditory hallucinations, derealization, feelings of pathological guilt, and obsessive preoccupations with death. Different diagnoses were made elsewhere, including postmenstrual psychosis, attention deficit disorder, bipolar affective psychosis, cycloid psychosis, and schizophrenia, for which she had been treated with several atypical antipsychotics that had resulted in a weight gain of more than 20 kg. At the age of 14 years, using the revised Wechsler Intelligence Scale for Children (WISC-R), a total IQ of 71 was established. Apart from an euthyretic struma, extensive somatic and neurological examination, including EEG and MRI of the brain, had not shown any abnormalities. At age 16, she was hospitalized to establish a definite diagnosis.

The patient is the second child of nonconsanguineous parents. Her mother has been treated with antiepileptics since her adolescence because of localization related epilepsy. The older sister of the patient has been diagnosed with idiopathic primary generalized epilepsy for which she is also treated with carbamazepine. In the 37th week of the pregnancy, the mother developed severe seizures despite maintenance therapy with carbamazepine. The delivery was uncomplicated and the patient's birth weight was 2800 g. Her developmental trajectory showed delayed milestones with walking from the age of 14 months and first speech of monosyllabic words at 2 years. Over the years, motor functioning remained clumsy. During her elementary school period, she followed a logopedic and motor training program. From the age of 10 years until menarche, there had been one short period during which the patient experienced weakness of the legs. During the 2 years prior to admission, there had been approximately 20 brief psychotic episodes.

At admission, all psychotropics (most recently olanzapine) had already been discontinued for some weeks during which time her body weight gradually normalized. Neuropsychiatric examination revealed no psychiatric symptoms. There were no facial dysmorphisms. Somatic or neurological dysfunctions were not found and laboratory tests were all normal. An MRI of the brain (3-Tesla) revealed no structural abnormalities. Neuropsychological assessment showed a total

IQ of 88 (Wechsler Adult Intelligence Scale–III [WAIS III]), increased distractibility, problems with inhibition, task switching, and planning, as well as reduced stress tolerance. An extensive clinical genetic work-up, including microarray analysis, revealed a small deletion at 16q23.3 that was not clinically relevant. A fetal anticonvulsant syndrome was ruled out (Department of Human Genetics, University Medical Centre, St. Radboud, Nijmegen).

During the hospitalization period, the patient experienced several short periods of psychotic symptoms, particularly auditory hallucinations, mood swings, affective instability, derealization, disorientation, thought disorder, anxieties, confusion, and paranoid and suicidal ideation. Although EEG recording after sleep deprivation during an interval without psychotic symptoms showed only one left frontal spike, a tentative diagnosis of extratemporal localization related epilepsy was made and the short lasting period with weakness of the legs during prepuberty, was considered retrospectively as an astatic seizure. Subsequently, the patient was treated with carbamazepine in a daily dose of 500 mg (plasma concentration 6.4 mg/L). Thereafter, pleomorphic psychotic episodes did not recur. A definite psychiatric diagnosis of postictal psychosis was made and the patient was discharged. Six months later she was hospitalized in a specialized epilepsy centre for a period of 3 months because of short periods of altered consciousness, affective instability, weakness of the legs, and fine muscle twitches in both arms and legs. The daily dose of carbamazepine was increased to 600 mg. A 24-hour EEG recording demonstrated, apart from the earlier identified left frontal spike, a sharp K-complex. During the complete hospitalization period, psychotic episodes did not occur and no etiological factors could be established. Treatment with carbamazepine was continued unchanged. During follow up over a period of 1.5 years, she remained free of psychotic symptoms and, apart from one short astatic seizure, epileptic phenomena no longer occurred.

## Discussion

Patient A, who presented at first admission with an acute confusional state, was initially diagnosed as suffering from bipolar affective disorder. Later, seizures provoked by changes in psychotropic medications occurred and these were followed by short periods of confusion and bizarre behavior. In patient B, a diagnosis of schizophrenia was made elsewhere. During a relatively long medication free clinical observation period, she developed relapsing brief psychotic episodes. Both patients made a full recovery from their atypical psychotic states and given their history

(A and B) and family load (B only), an epileptic origin was suspected. Although EEG recordings demonstrated only minimal epileptic activity in both patients, a tentative diagnosis of epilepsy was made and treatment with antiepileptics was started. Thereafter, they remained free of epileptic and psychotic symptoms.

Since in patient A seizures had most probably occurred already in late adolescence, during which she had never used psychotropics, psychopharmacologically induced kindling leading to psychotic states could be ruled out.<sup>17,18</sup> Neither of the patients had previously been treated with antiepileptics, for which reason the phenomenon of a forced normalization associated psychosis can be excluded. In addition, neither the EEG recordings nor the clinical presentations in patients A and B met the criteria as proposed for this condition.<sup>17</sup> A limbic psychotic trigger reaction (LPTR), as hypothesized by Pontius et al is also very unlikely because both patients showed disorientation during the act and amnesia for the act, in the absence of the typical out of character, bizarre, unplanned involuntary behaviors that are associated with LPTR.<sup>19,20</sup>

Because the ictus-related relapsing psychotic states with full recovery had a kaleidoscopic clinical picture, in both patients a definite diagnosis of postictal psychosis was justified. Interestingly, in both of the patients, sleep disturbances were the initial presenting symptom of the postictal psychosis. This phenomenon has been established via several observations and is recognized as a typical prodrome.<sup>21–23</sup> No specific risk factors were present in either patient, although in patient B a family history with epilepsy, but not psychiatric diseases, was present.

The phenomenology of the postictal psychosis, that comprises affective, schizophrenic, and confusional elements, may be referred to as a schizophrenia-like psychosis, but its atypical and highly variable psychopathological picture fits best with the criteria for a cycloid psychosis. These include, apart from a subacute onset, symptoms like confusion expressed as perplexity, hallucinatory experiences, mood swings, paranoid ideation, and pervasive experience of anxiety.<sup>24–27</sup>

With respect to the treatment of a postictal psychosis, optimal seizure control is the primary target, whereas in the acute phase a low dose of an antipsychotic for a restricted time frame may be applicable.<sup>5,28</sup> Treatment of epilepsy with concomitant psychotic symptoms may, however, be complicated since antipsychotics have the propensity to induce seizures and because several anticonvulsants, especially topiramate, levetiracetam, and vigabatrin, may precipitate psychosis.<sup>29–31</sup>

The diagnostic foginess as demonstrated in the patients reported in this study is exemplary of the major caesura that history has drawn between neurology and psychiatry.<sup>32</sup> As a consequence, both the clinical diagnostic awareness of psychiatric manifestations of neurological diseases as well as the process of pharmacological treatment is endangered in patients presenting with (relapsing) atypical psychiatric symptoms.<sup>33</sup> Therefore, as advocated by several authors over the past decade, it is important to reintegrate neuropsychiatry into mainstream psychiatry in an attempt to close the divide between psychiatry and neurology.<sup>34–36</sup>

## Disclosures

The authors report no conflicts of interest in this work.

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