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Guidelines

Guidelines for recognition and treatment of the psychoses associated with epilepsy

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Abstract

Epilepsy and psychiatric diseases are frequent comorbidities. Psychoses in patients with epilepsy have special physiopathology and several clinical presentations and prognoses. Their treatments are also specific, according to the specific diagnosis. This paper represents the summary of a consensus meeting held in November 2003 by a Belgian French-speaking group of neurologists, neuropediatricians and psychiatrists and proposes guidelines for the recognition and treatment of those entities.

Key words : Psychosis ; epilepsy ; antipsychotics.

Introduction

Psychiatric disturbances have long been associated with epilepsy (1, 2). The clinical spectrum of these disturbances encompasses chronic depression and anxiety disorders, personality disorders, post-ictal depression, post-epilepsy surgery depression and the group of psychoses associated with epilepsy. There is still a controversy as to whether the prevalence of psychiatric disorders is increased among epileptic patients (1, 2, 3, 4), but there is a growing body of evidence (4, 5) suggesting an over representation of psychotic illnesses, the current estimates being 2 to 7% (6), particularly schizophrenia-like psychosis, among the population of epileptic patients. The aim of the present article is to briefly describe the several forms of psychoses specifically associated with epilepsy and to draw the therapeutic attitudes which can be proposed, as a result of a consensus meeting held in November 2003 by the Belgian French-speaking group of the reference centres for refractory epilepsy.

Clinical characteristics of psychoses related to epilepsy

Among the numerous psychiatric disorders seen in epilepsy, the so called psychoses of epilepsy are a mixed bag in which several distinct entities can be distinguished on clinical grounds. These various psychoses are mostly episodic or transient, linked to seizure activity or seizure control (by medications, surgery or vagus nerve stimulation) and contrast with a chronic non-episodic schizophrenia-like psychosis (Table). The main risk factors for developing psychosis are considered to be duration of epilepsy, temporal lobe seizures, refractory epilepsy, multiple seizure types, polytherapy and poor compliance (6). Diagnostic work-up includes evaluation of the clinical situation (notably seizure count), antiepileptic drugs (AEDs) plasma level and electroencephalogram (EEG).

The so-called "ictal psychosis" is an expression of ongoing seizure activity representing non convulsive status epilepticus (absence status or complex partial status) and may frequently present under the form of obtundation or delirium. It is not a psychotic state par se and should be handled with adequate anti-epileptic drugs

Post-ictal psychosis

Psychiatric symptoms can transiently occur post-ictally in up to 10% of patients (7, 8) and may represent a post-ictal exacerbation of interictal psychiatric problems. In rare instances, post-ictal psychiatric symptoms may concentrate in such intensity as to give rise to a full blown post-ictal psychosis (PIP), usually after a cluster of seizures of unusual importance. After a typical "lucid interval" of 3 to 72 hours between the last seizure and the onset of the psychiatric symptomatology, an acute psychotic episode made of affective, schizophrenic and confusional and hallucinatory elements supervenes. Mood symptoms include lability, grandiosity, depression, fear and sensation of impending death. The episode will resolve spontaneously within a few days (up to 2 weeks), though it can be shortened or alleviated by benzodiazepines and/or antipsychotics (9). Some authors have stressed the

Table 1

Clinical classification of psychoses related to epilepsy

Type of psychosis	Relation to seizures	Duration	EEG	Treatment
"Ictal psychosis"	During status epilepticus	Minutes to hours	Ictal (non convulsive status)	Benzodiazepines Antiepileptic drugs
Postictal psychosis	After a flurry of seizures & a lucid interval	Days to weeks	Postictal slowing to usual	Benzodiazepines Antipsychotics
Alternative psychosis	When seizures are decreased or suppressed	Weeks to months	Better or normalised	Antipsychotics Seizures by lowering AEDs
Chronic schizophrenia-like psychosis	No specific relation to seizures	Years	Mostly abnormal	Antipsychotics

fact that PIP is heralded by severe insomnia which, were it recognised, would allow preventive treatment of the episode (7) by prompt administration of low doses of benzodiazepines or antipsychotics. Post-ictal psychosis represents about 25% of psychotic states associated with epilepsy (6).

Alternative psychosis

Landolt (10) was the first to describe an inverse relationship between psychosis and epilepsy : as some patient's epilepsy improved and eventually came under control with adequate anti-epileptic medications, and as their EEG became devoid of interictal epileptiform features, their psychiatric status deteriorated, to reach a stage of true psychotic state. Landolt used the term "forced normalisation" but the clinical entity is nowadays most commonly called alternative psychosis. This term illustrates the inverse relationship between seizure control and the occurrence of psychotic symptoms. The most frequent manifestation is a paranoid psychosis without clouding of consciousness and with a richness of affective symptoms. Alternative psychosis is not common, its prevalence being estimated to be around 1% of epilepsy cases (11). Some authors (12) consider that alternative psychotic episodes should be treated by reducing or discontinuing anti-epileptic drugs until seizure recurrence causes a remission of psychotic symptoms. However, alternative psychosis is an episodic phenomenon : it is limited in time and its natural evolution is towards remission (for more details about pathophysiology and diagnostic criteria see 13). Before considering the diagnosis of alternative psychosis as established, one should pay attention to the possibility of an iatrogenic effect of the anti-epileptic drugs.

Psychosis induced by anti-epileptic treatment

Psychosis has been reported as a rare but major side-effect of virtually all anti-epileptic drugs (AEDs). These include the standard AEDs as well as the newer AEDs like vigabatrin (14), lamotrigine (15, 16), topiramate (17), tiagabine and levetiracetam (18). AED-related psychoses are not strictly speaking a form of psychoses of epilepsy but they should be taken into account in the differential diagnosis with alternative psychosis.

Psychoses have also been reported after temporal lobectomy (19, 20, 21) and more specifically after resection of ganglioglioma or dysembryoplastic neuroepithelioma (22), or more often after removal on the right side (21). Although less frequent than postoperative depression which occurs in about 25% of patients (23), psychosis is undoubtedly the most severe psychiatric complication. Trimble has made a mean estimate of 7.6% of de novo case incidence in patients undergoing temporal lobectomy for intractable epilepsy (24) and suggested that in some cases an alternative psychosis phenomenon was likely. Some studies suggest that surgery over the age of 30 years (25) and a family history of psychosis (21, 25) are risk factors for the development of postoperative psychosis.

Chronic schizophrenia-like psychosis of epilepsy (SLPE)

This chronic condition occurs in at least 3% of epileptic patients (3, 4, 5, 26, 27) and accounts for 10 to 30% of psychosis cases associated with epilepsy (6), usually starting more than 10 years after the onset of the epileptic disease. The schizophrenia-like psychosis of epilepsy shares some common features with classical schizophrenia but tends to show less negative symptoms, better premorbid function, less deterioration of personality and possibly a better outcome after treatment (28). Slater *et al.* emphasised the fact that "the delusions and hallucinations of patients with SLPE were empathizable (the patient remains in our world)" (29). This is a non-episodic or chronic interictal psychosis which occurs independently of seizures, though it tends to happen in long lasting refractory epilepsy.

Treatment

Use of antipsychotic drugs is the mainstay of the therapeutic approach of psychoses and it seems difficult, if ever possible, to avoid their use in the psychoses associated with epilepsy, either in the acute stage or for protracted periods. However antipsychotics are dopamine antagonists and are known to have proconvulsant properties. Therefore a careful and somewhat astute strategy appears desirable. When using antipsychotics and antidepressants, one should try to avoid agents known to be associated with a relatively greater risk of lowering the seizure threshold (clozapine, chlorpromazine ; clomipramine, maprotiline, bupropion) (30). The potential seizure-threshold lowering properties of psychotropic drugs tend to be related to the dose as well as to the speed of escalation. Fortunately, some patients will respond to low doses.

We recommend antipsychotics known or supposed to have low epileptogenic properties (31) :

– olanzapine (Zyprexa), 5 to 25 mg/d
– risperidone (Risperdal), 0.5 to 6 mg/d
– quetiapine (Seroquel), 50 to 600 mg/d
– amisulpride (Solian), 50 to 800 mg/d

Caution in their use should be exercised since some (more than others) are associated with a weight gain and an increased risk of diabetes and dyslipidemia (32).

Clozapine (Leponex) has a relatively high epileptogenicity (30, 31) and its use in epilepsy is not generally recommended. It is advised to start with low doses and escalate slowly.

In the USA, molindone (Moban) is used because of its very low apparent epileptogenicity, 50 to 200 mg/d.

There are at present atypical (second generation) antipsychotic drugs available for IM administration :

– olanzapine (Zyprexa), with effectiveness starting after 15 minutes
– droperidol (Dehydrobenzperidol)
– risperidone (Risperdal Conta), with a relatively long delay of action (not very useful in emergency situations).

In acute need, IV route can be performed with :

– haloperidol (Haldol) IV, 2 to 5 mg, sometimes in association with benzodiazepines.
– droperidol (Dehydrobenzperidol) IV, 2,5 to 5 mg, sometimes in association with benzodiazepines.

Benzodiazepines have a limited use, and seem to be optimal when associated with antipsychotics, in acute situations (for instance in post-ictal psychosis) :

– lorazepam (Temesta), 0.5 to 2 mg
– clobazam (Frisium), 10 to 60 mg

Antidepressants are not a first choice treatment of acute psychosis but can be useful in the treatment of epilepsy patients with depression and irritability (30). Selective serotonin reuptake inhibitors (SSRIs) are most commonly recommended. It is advised to choose agents minimising interactions with liver microsomes :

– sertraline (Serlain), 25 to 100 mg/d
– citalopram (Cipramil, Citalopram), 10 to 40 mg/d
– paroxetine (Seroxat), 10 to 30 mg/d
– escitalopram (Sipralexa), 5 to 20 mg/d

In patients who do not respond well to SSRIs an alternative is :

– venlafaxine (Efexor), 75 to 225 mg/d

These antidepressants may lower the seizure threshold and the rapidity of dosage escalation appears to be a factor. It is therefore advised to start with a low dose and escalate slowly. Tricyclic antidepressants are reportedly more epileptogenic and should be used with utmost caution.

Buspirone (Buspar) is a serotonin 1a partial agonist originally used as an anxiolytic. Some authors recommend it as an effective treatment of aggression (30), 10 to 60 mg/d.

Electroconvulsive therapy (ECT) is acknowleged as potentially beneficial in the setting of schizophrenic psychosis refractory to antipsychotics (33). It may therefore be deemed desirable in some cases of SLPE since this instance of psychosis associated with epilepsy is a chronic, sometimes resistant, condition. ECT is not contraindicated by the presence of epilepsy if the psychopathological condition makes it necessary (34).

Conclusion

There is a general agreement that psychopathology is over-represented in epileptic patients. Psychotic states are not infrequently encountered in the care of epileptic patients. The specific types of psychoses can be delineated on clinical grounds. They have a specific prognosis and deserve as well a specific treatment. Awareness of these syndromes will allow their prompt recognition and care, and therefore is of potential benefit for the well-being of these patients.

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