The psychoses of epilepsy

People who have epilepsy seem particularly liable to certain major psychiatric disorders: a chronic interictal psychosis that closely resembles schizophrenia; and episodic psychotic states, some of which may arise in close temporal relation with seizure activity. These disorders are conventionally referred to as the psychoses of epilepsy although some of the episodic forms would be more accurately described as acute confusional states. These conditions have for long puzzled and intrigued psychiatrists and neurologists, but in recent years this interest has quickened especially among biologically minded psychiatrists in search of a neurological model for schizophrenia. In the psychoses of epilepsy and in schizophrenia converging lines of enquiry in neuroimaging and in neuropathology in particular, have implicated the mesial temporal structures, the more so in the dominant hemisphere, and comparable abnormalities have been reported. This review will seek to identify areas of progress, areas of difficulty, and persisting dilemmas.

Epilepsy and schizophrenia

The precise nature of this relation has taxed clinical observers since before the turn of the century. Over the past four decades a consensus has begun to take shape—namely, that certain forms of epilepsy may act as risk factors for the subsequent development of a chronic interictal psychosis, a syndrome sometimes referred to as the schizophrenia-like psychoses of epilepsy (SLPE). This psychosis does resemble schizophrenia in its phenomenological manifestations, pursues a similar course, is as responsive to antipsychotic medication, and is largely uninfluenced by concurrent seizure activity. Given these similarities it is reasonable to question whether this comorbidity could not have arisen as a result of a chance association between two relatively common disorders. The answer should lie in community based comparisons of unbiased samples of epileptic and non-epileptic subjects with respect to prevalence of psychosis. Attempts have been made to do this, yielding a prevalence of schizophrenia within an epileptic population that varies between 3% and 7% (prevalence in general population 1%). However, a failure to use strictly defined and internationally recognised diagnostic criteria for schizophrenia and to distinguish between SLPE and episodic psychoses may have resulted in a spurious inflation in the prevalence figures. In the past year two studies that have to some extent redressed this difficulty have been published. In Iceland a case controlled study found that although there was no excess of psychiatric illness in epileptic subjects, among those who were psychiatrically ill a disproportionate number were psychotic. In Denmark Bredkjaer et al used two national inpatient registers for epilepsy and for psychosis respectively to compare the subsequent incidence of schizophrenia in patients who had at some point undergone admission to hospital for epilepsy with that in the general population. A standardised incidence ratio of 1.48 for all epilepsy and 2.35 for psychomotor epilepsy argues strongly for epilepsy as a risk factor for schizophrenia, but an epilepsy sample defined by need for inpatient care may be considered unrepresentative. Although vulnerable to similar criticism, the neurology clinic based study of Mendes et al report convincing data. The prevalence of schizophrenia, diagnosed according to DSM3R criteria, was nine times greater among clinic attenders with epilepsy than those with migraine. Taken together these studies provide strong, though far from conclusive evidence, that the SLPE is a unique disorder and not an artefact of random association. The definitive epidemiological study is still awaited. Meanwhile other approaches could be explored: if the SLPE is indeed a secondary or symptomatic psychosis the prevalence of schizophrenia among family members should not greatly exceed the prevalence in the general population. It should certainly fall short of that found in the families of schizophrenic probands. Early studies—for example, that of Slater and Glithero, suggest that this is the case, but as yet no family history study using state of the art methodology has been published.

Even if it is conceded that epilepsy may be a risk factor for the development of schizophrenia, it is clear that the great majority of those with epilepsy do not become psychotic. Are there epileptic characteristics that predict such a development? It has long been held that temporal lobe epilepsy, more so than idiopathic generalised epilepsy, is a risk factor for psychosis, although this has been contested on the grounds that the finding is based on data derived from specialist epilepsy clinics in which temporal lobe epilepsy is overrepresented. However, recent data, some of it epidemiologically derived, continue to support this conclusion. Flor-Henry first reported an association between left sided temporal lobe epileptic foci and SLPE. Subsequent work has also noted, albeit inconsistently, a laterality effect, but this must be balanced against the finding that in large, relatively unselected samples, left sided foci predominate in a ratio of 60:40. The neuropathology of the epileptogenic lesion may be relevant, but is unlikely to be of major effect: in one large neurological series four out of the nine patients with gangliogliomas developed a psychosis, but this group still only accounted for 15% of the psychotic series. Andermann and reported a further six cases, but these seem to have
and ictal fear (complex partial seizures containing fear as a postictal psychotic subjects report more seizure clustering\(^1\).\(^7\) Most of the risk variance for SLPE still remains unexplained, but it must be remembered that even if it is accepted that epilepsy may increase the likelihood of schizophrenia, any sample of patients with SLPE will include a proportion, unfortunately unidentifiable, the presence of which is due to chance association; this group will act as a confounding factor in any search for aetiology.

The episodic psychoses
The most common by far are the postictal psychoses. Others include some drug induced psychoses and the alternating psychoses that arise during periods of improved seizure control. The salient features of postictal psychoses have been consistently reported (for example, see Logsdail and Toone\(^7\)\(^9\)). They usually follow exacerbations, especially clusters, of complex partial seizures, sometimes without but more commonly with generalisation. Characteristically, cessation of seizure activity is followed by a brief interlude—a “lucid interval”—of 12-72 hours before the mental state deteriorates. The psychosis, which comprises affective, schizophrenic, and confusional elements, may last for up to a week. The EEG may exhibit increased epileptic discharge activity or a slowed dominant rhythm. The episodes resolve spontaneously, but often recur, usually displaying similar phenomenology.

The same question that was asked of the SLPE may also be asked of the postictal psychoses: what factors predispose the minority of epileptic patients to develop postictal psychoses? Although a far from uncommon disorder, postictal psychoses have received considerably less attention than SLPE and many of the accounts that have been published describe an iatrogenic psychosis that occurs for the first time after an increase in seizure activity due to anticonvulsant withdrawal during presurgical evaluation. Although such studies may be informative, particularly as they are prospective and accompanied by telemetric information, the cases they describe are likely to be unrepresentative of the spontaneously occurring postictal psychoses. Some centres report an association between complex partial seizures and postictal psychoses\(^4\)\(^5\)\(^7\); others fail to do so.\(^8\) Postictal psychotic subjects report more seizure clustering\(^7\) and ictal fear (complex partial seizures containing fear as a major component).\(^8\)\(^9\) Bilateral EEG discharges are seen more often in subjects with postictal psychoses than non-psychotic controls.\(^10\)\(^11\) Compared with SLPE, both age of epilepsy onset\(^11\) and psychosis onset\(^1\) are delayed.

Other forms of episodic psychosis are distinctly uncommon. The phenomenon of forced normalisation, whereby improved seizure control, usually as a result of change of anticonvulsant medication, is associated with a “normalisation” of the EEG and the emergence of psychotic features, may underlie some episodes of psychotic behaviour, particularly those associated with the introduction of novel antiepileptic drugs. As first described by Landolt, forced normalisation occurred in the context of partial epilepsy, but more recent accounts implicate the succinimide group in the treatment of primary generalised epilepsy.\(^12\) The use of vigabatrin\(^13\) and zonisamide\(^14\) may also carry an increased risk of psychotic disturbance.

Psychosis and temporal lobectomy
In the early days of temporal lobe surgery for treatment of epilepsy the psychiatrically unwell made up a significant proportion, sometimes most of those who went forward for surgery. One in six was psychotic. There was then a hope, even an expectation, that surgery might benefit psychosis as it had epilepsy. This was not borne out and the proportion of epileptic patients with psychosis has gradually fallen. But as one author has pointed out, it might still be considered better to be psychotic without seizures than to be psychotic with them.\(^15\) Chronic schizophrenia need not be a contraindication and carefully selected patients may benefit from surgery.\(^16\) A history of postictal psychoses should be considered a positive indication for surgery. Psychosis may present for the first time—“de novo psychosis”—after surgery. The condition was noted in early surgical series, but has recently received greater attention. It is difficult to know whether this represents a true increase in incidence, better recognition, or a fall in the age of surgery. The de novo psychoses are a mixed bag: some are depressive in character, some schizophrenic; some pursue a chronic course, some are episodic, the de novo postictal psychoses forming a definite subgroup.\(^17\) Their aetiology may be similarly diverse. In some the development of psychosis may be predetermined by earlier events and the surgical procedure an irrelevant artefact. In a few cases seizure control may lead to forced normalisation and an alternating psychosis. Only one feature stands out clearly preoperatively the presence of SLPE is associated with a left temporal focus; 85% of de novo psychoses follow right temporal surgery. The reasons for this are unclear. There is some indication,\(^18\) hardly yet substantiated, that depression is commoner after right sided lobectomy. The amount of resected tissue is also more generous.

Aetiology of the epileptic psychosis
Epilepsy and psychosis may each arise out of some form of cerebral dysfunction common to both; or psychosis may be a consequence of seizure activity. The first seems more likely. Most forms of epileptic psychoses occur more commonly in the partial epilepsies, especially complex partial seizures. Within the surgical series patients with developmental lesions may be at particular risk. Parallels have been drawn between anomalies of cerebral architecture in schizophrenia and the epileptogenic cortical dysplasias\(^19\) but in clinical practice such associations have yet to be reported. Distinctive patterns of hypometabolism/hypoperfusion have been reported\(^20\) but with no consistency. Dominant hemispheric temporal lobe involvement may be associated with a more pure form of SLPE.\(^21\) The role of seizure activity finds its theoretical justification in the kindling hypothesis but in humans even the kindling of epileptic seizures remains debatable. There is no precedent for the kindling of behavioural change. Liability to SLPE is not related to seizure frequency or severity; indeed it often occurs at a time when seizure frequency is declining. However, the extent of mesial temporal and, particularly, extratemporal damage may be a risk factor. Recent neuroimaging data suggest that mesial temporal lesions may be associated with loss of tissue volume and with neuronal damage in areas well beyond the temporal lobes including the striatum, thalamus, and frontoparietal grey matter.\(^30\) Reductions in hippocampal volume, tissue damage, and neuronal loss may be progressive and may reflect the duration of epilepsy.\(^31\)\(^33\) Function may also deteriorate with chronicity.\(^34\) Extratemporal neuronal damage may also occur\(^35\) although it may be reversible. Brutton et al\(^36\) reported ventricular enlargement, periventricular gliosis, and white matter abnormalities in epileptic patients with psychosis compared with those without. Subjects with SLPE have
smaller whole brain and bilateral hippocampal volumes compared with matched non-psychotic epileptic controls (Mellers et al, personal communication). The association between degree of damage and chronicity may explain the time interval between onset of seizures and onset of psychosis in both SLPE and postictal psychoses. In conclusion, an accumulation of admittedly less than perfect evidence strongly suggests an environmental rather than a genetically determined form of psychosis. The aetiology, like that of schizophrenia itself, will in all probability prove to be multifactorial with no one factor predominating.

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EDITORIAL COMMENTARY

Isolated Horner’s syndrome and syringomyelia

How far do you investigate the isolated Horner’s syndrome? The sympathetic pathway to the pupil is long originating in the hypothalamus from where the central neuron descends to the intermediolateral column of the upper three dorsal spinal segments. The preganglionic neuron then ascends to the superior cervical ganglion and the postganglionic neuron travels from there via the internal carotid artery to the eye. There is little evidence of degeneration and thus Horner’s syndrome has long been known as a good localising sign but a poor localising sign.

Individual case reports relate isolated Horner’s syndrome to various diseases including malignancy at the lung apex, dissection, arteritis or trauma of the internal carotid artery, jugular venous ectasia, and migraine or cluster headache. The paper by Kerrison et al (this issue, pp 131–132) adds syringomyelia to this list of possible causes of isolated Horner’s syndrome and recommends that any such patient in which the lesion is thought to be of the central or preganglionic neuron should be investigated by MRI of the brain and cervical cord.

The available literature does not make it easy to develop a rational approach to the investigation of isolated Horner’s syndrome. The incidence of central Horner’s syndrome varies from 2.5% in ophthalmological reviews to 63% in the neurological literature. Preganglionic Horner’s syndrome represented 21% of a neurological series and 67%
of an ophthalmological series. Most series agree that vascular disease is the usual cause of central Horner’s syndrome and that trauma or tumour explains most preganglionic lesions. Postganglionic lesions occur in between 0.5% and 57% of patients reported and arise from various pathologies including vascular disease and tumour.

The localisation of the lesion by clinical and pharmacological means is important and influences the need to investigate. To neurologists clinical localisation is a familiar task, pharmacological localisation less so. In practice most cases of Horner’s syndrome are not truly isolated and the association of neighbourhood symptoms or physical signs and the extent of any sweating impairment will enable the lesion to be placed with some precision. When this is not possible the use of cocaine and pholedrine eye drops can be helpful in determining the direction of investigation, the depth and pace of which is aimed at the rapid diagnosis of conditions in which intervention may alter the natural history. Thus diagnosing an apical bronchial carcinoma or dissection of the carotid artery is of potentially greater immediate importance than the diagnosis of syringomyelia.

Clinical assessment, pharmacological localisation, and imaging enable the full assessment of cases of isolated Horner’s syndrome. How far and how fast we should undertake this process will be influenced by the clinical presentation and the local availability of investigative facilities.

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