Common Psychiatric Comorbidities in Epilepsy: How Big of a Problem is it?

[1]Jay A. Salpekar and [2]Marco Mula

[1]Kennedy Krieger Institute, Johns Hopkins University

[2]Institute of Medical and Biomedical Education, St George's University of London and the Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

Corresponding author:

Jay A Salpekar

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Abstract: Psychiatric illness and epilepsy commonly co-occur in adults and in children and adolescents. Theories of comorbidity are complex, but recurring associations between the conditions suggest overlap that is more than simple co-occurrence. Common underlying pathophysiology may imply that epilepsy itself may constituently include psychiatric symptoms. Conditions such as depression or cognitive difficulties commonly occur and in some cases are considered to be associated with specific epilepsy characteristics such as localization or seizure type. Regardless of etiologic attributions to psychiatric comorbidity, it is clear today that treatment for epilepsy needs to target psychiatric illness. In many cases, quality of life improvements depend more upon addressing psychiatric symptoms than seizures themselves.

Key Words: psychiatry, epilepsy, depression, cognitive, comorbidity, behavior, diagnosis

Introduction

Psychiatric comorbidities have long been studied in the context of epilepsy. A sizeable body of evidence supports the understanding that psychiatric illness is overrepresented in epilepsy as compared to other chronic medical illnesses (1). Even with the markedly altered functionality and lifestyle associated with conditions such as cancer, diabetes, or asthma, the presence of psychiatric comorbidity in epilepsy appears to be more substantial (2). Although opinions regarding the best methods of diagnostic assessment may differ, comparable assessment tools clearly find that the overrepresentation of psychiatric illness is significant both in adults and in pediatrics (3, 4).

Nevertheless, a persisting challenge is in measuring the presence of comorbidity independent of possible confounding factors. Very few studies assessing comorbidity are prospective in nature or have a population based approach. Additionally, the broad spectrum of illness makes it difficult to isolate psychiatric symptoms from underlying medical or neurologic illness. The epilepsy population itself is heterogeneous, so overlap with heterogeneous and somewhat arbitrarily categorized psychiatric conditions may hinder a comprehensive diagnostic approach. Still, even with these challenges, the connection between psychiatric illness and epilepsy is abundantly present, especially for mood disorders and problems of cognition.

What remains unclear is how epilepsy related characteristics may be etiologically associated with psychiatric comorbidity. While it has been long considered intuitive that the more severe the epilepsy, the more severe the comorbidity, this may not be completely accurate. It may be that specific seizure related characteristics affect the presence or absence of comorbidity. Seizure frequency is commonly viewed as adversely impacting psychiatric state, as is the usage of multiple anticonvulsant medications, thus adding to the potential risk of developing psychiatric illness. However, neither context may represent the essence of comorbidity in the truest sense.

Ultimately, it may be that epilepsy is a broad spectrum illness with heterogeneity that includes psychiatric aspects. In that sense, thinking of comorbidity as the association of two etiologically unrelated conditions would be inaccurate. Certain types of epilepsies could have psychiatric, cognitive or behavioral complications that are inherently associated with a common underlying pathophysiology. With that approach, comorbidity would not exist; instead, the associated behavioral symptoms would be viewed simply as constituent parts of the epilepsy.

Such a paradigm shift has marked implications in terms of treatment. Despite the intrigue in thinking of comorbidity in this manner, it is a modern approach, and as such the evidence base for treatment is underdeveloped. Treatment studies and clinical trials are not typically conceptualized in this way. However it seems clearer now that in order to comprehensively treat epilepsy and to improve quality of life, both behavioral and seizure specific outcomes need to be addressed. Even though this paradigm does not reflect the state of the evidence at this time, the approach of identifying psychiatric symptoms independently is still meaningful as a first step in management. The evidence base does help us in that regard, and will be reviewed in the following sections.

COMMON COMORBIDITIES IN ADULTS

Epidemiological aspects in adults with epilepsy

Mood disorders

Cross-sectional, population-based studies in adults with epilepsy are showing a uniformly increased prevalence of depression, with prevalence rates very similar to those of the general population only among seizure free patients (5), while the prevalence is definitely higher than that in unselected samples (between 17% and 22%) (6), and it is up to 55% in patients with drug-resistant epilepsy (7). In general terms, these figures partially reflect the severity of the underlying seizure

disorder not only in terms of psychosocial difficulties but also in terms of brain dysfunction. Cross-sectional studies are highly informative from a public health perspective, as they give an idea of the size of the problem, but cohort studies can provide information on the temporal relationship between comorbid conditions. In fact, a number of studies are now suggesting that the relationship between epilepsy and depression is not necessarily unidirectional and patients with depression are at increased risk of developing epilepsy as well. Data from the UK General Practice Research Database show that the incidence-rate ratio of depression is significantly higher during the three years preceding the onset of epilepsy (8). A study from Sweden shows that the age-adjusted odds ratio for the development of epilepsy is 2.5 for patients with a depressive disorder (9) and these figures have been confirmed by at least other three studies with an increased risk up to 7-times in selected cases (10-12). All these data clearly suggest that either some patients with depression develop epilepsy as part of the "natural course" of the depressive disorder or that depression is a premorbid phase of some epileptic syndromes.

Anxiety disorders

Data on anxiety disorders are less systematic than those on depression and this is due to a number of reasons including, the high prevalence of depression in epilepsy that can mask anxiety disorders, a common attitude among neurologists in considering anxiety as the natural consequence of having unpredictable seizures and the potential misdiagnosis between panic attacks and seizure-based phenomena like ictal fear. As already discussed in the context of depression, the few available studies suggest a uniformly increased prevalence of all anxiety disorders (13). Two US National surveys show that people with self-reported epilepsy are two times more likely to report a diagnosis of anxiety disorder than those without (14, 15). These figures have been replicated by another cross-sectional, population-based study in unselected patients with epilepsy using standardised clinical interviews (16).

Although less established as compared to depression, a few preliminary studies are suggesting a similar bidirectional relationship between epilepsy and anxiety disorders. A US study in veterans older than 65 show that a previous history of anxiety is significantly more common in those who developed epilepsy as compared to controls (17). A population-based, case control study in Sweden show that patients hospitalised for anxiety disorders are more than 2 times at increased risk of developing unprovoked seizures (9). Finally a cohort study using data from the UK General Practice Research Database show that the incidence for anxiety disorders is not only higher in people with epilepsy as compared to controls but it is already increased three years prior to the diagnosis of epilepsy (8).

Psychoses

Psychoses and thought disorders are less frequent than mood and anxiety disorders but they represent serious complications affecting prognosis, morbidity and mortality in epilepsy. In general terms, epidemiological studies show that the prevalence of psychoses is 7 times higher than that of schizophreniform disorders in the general population (18). Psychotic symptoms in epilepsy are well recognised in a number of different clinical scenarios, from post-ictal psychoses (19), to antiepileptic-drug related psychotic episodes (20), to chronic schizophrenia-like disorders (21). The prevalence of psychoses in epilepsy seems again related to the severity of the seizure disorder but also to the degree of pathology of the temporo-limbic structures. Cross-sectional, population-based studies in unselected samples show that the prevalence of non-organic, non-affective psychoses, including schizophrenia and related disorders, is around 4%-5% (9, 22) but in selected samples, such as hospital case series, is even higher than that (23). A systematic review and meta-analysis of published literature pointed out that patients with temporal lobe epilepsy present with the highest prevalence, in the region of 7% (24). In patients with temporal lobe epilepsy, those with febrile seizures and hippocampal sclerosis are more

likely to develop psychoses than those with normal or minimal changes at the MRI (25). Interestingly, both a family history of psychoses and a family history of epilepsy have been identified as potential risk factors suggesting a strong neurobiological connection between epilepsy and psychoses [18]. As already discussed in the context of depression, psychoses have also shown a bidirectional relationship with epilepsy. A case-control study in Sweden shows that the age-adjusted odds ratio for seizures is 2.5 in patients with any diagnosis of psychosis even after controlling for antipsychotic drug treatment and other potential confounding factors (9). Two retrospective cohort studies show that patients with schizophrenia have a 2 to 3 times increased risk to develop epilepsy (26) with incidence rates of 7 per 1000 person-year (27).

Cognitive problems

Cognitive problems represent a significant burden for any neurological disorder. Despite the large amount of epidemiological studies in children with epilepsy, there are no population-based studies investigating the neuropsychological status of people with adult-onset epilepsy (28). This obviously represents a serious omission in the scientific literature as the issue of cognitive problems is not just for children and young people but also for adults. In fact, a subjective impairment in cognitive functions is frequently reported by adult patients and ranging between 44% and 59% (29). Most importantly, 63% of patients perceive that antiepileptic drugs prevent them from achieving goals in life rather the epilepsy itself (30). The problem of neuropsychological deficits in adult-onset epilepsies is quite complex. Several studies have clearly shown that subjective memory complaints do not correlate with formal neuropsychological deficits but are rather due to other factors, especially anxiety and depression (31, 32). Antiepileptic drugs have a different propensity for cognitive side effects but a number of different variables, which are both patient-related and epilepsy-related, have to be taken into account in adults (30).

Patients are often concerned that the epilepsy may be responsible of accelerated brain aging. Although population-based studies in this area are lacking, it has been suggested that the potential cognitive decline in aging patients with epilepsy is very slow and the cognitive performance at the onset of the epilepsy is the most important variable (28, 33). It has been suggested that people with epilepsy may reach a clinically significant threshold of impairment late in life because they start at a lower baseline cognitive level than healthy subjects rather than because of a true accelerated cognitive decline (33). This would be further supported by studies in newly diagnosed adult patients with epilepsy showing that they are cognitively compromised even at the onset of the disorder and before starting antiepileptic drug treatment (34). Further studies in this area are urgently needed.

Psychiatric comorbidities as a poor prognostic marker in adults with epilepsy

The amount of epidemiological data on psychiatric comorbidities of epilepsy has increased the attention of clinicians and researchers on the potential impact of comorbidities on the prognosis of epilepsy and the identification of potential biomarkers (35). As already discussed, the different prevalence rates in different epilepsy populations, namely seizure free and drug-resistant patients, seems to suggest that the presence of psychiatric comorbidities partially reflects the severity of the seizure disorder. In adults with epilepsy, there is now enough literature supporting the hypothesis that psychiatric comorbidities represent also a poor prognostic marker.

It has been established long time ago that depression is a better indicator of quality of life than seizure frequency itself (36). It is now becoming evident that depression is also associated with poor response to the antiepileptic drug treatment (37, 38), poor outcome after epilepsy surgery (39, 40), increased seizure severity (41), increased risk of injury (42) and premature mortality (43). Future studies

need to clarify whether early identification and prompt treatment of psychiatric comorbidities can have an impact on the prognosis of the epilepsy or whether they just represent indicators of poor prognosis.

COMORBIDITIES IN PEDIATRICS

Psychiatric comorbidity has historically been less well studied in pediatrics than in adults. However, recent high quality population studies offer detailed information regarding the amount of medical and psychiatric comorbidity in pediatric epilepsy. A recent study of a Norwegian patient registry showed that 78.3% of the pediatric epilepsy population had comorbid medical, neurologic or psychiatric illness as compared to 30.3% of the general pediatric population (44). Developmental or psychiatric disorders were present in 42.9% of children with epilepsy, and higher if the epilepsy was deemed complicated. Although the diagnoses were not verifiable beyond the initial medical record notation, the sample size of over one million is notable and reinforces the notion that psychiatric comorbidity is significant in the large population of persons with epilepsy.

Sizeable comorbidity has also been found in a large scale retrospective study of newly diagnosed epilepsy. Administrative review of over six million records found 7654 children with newly diagnosed epilepsy. Neurobehavioral comorbidities were present in 60% of these children as compared to 23% without epilepsy (45). These recent studies complement existing information in the adult population and affirm that comorbidity is markedly present in children as well as in adults. Furthermore, in children, the comorbidity may be more readily measurable and thus stimulate valuable insight into theories of pathophysiologic overlap.

<u>Behavioral Side Effects of Anticonvulsants</u>

A common question, especially in children, is whether anticonvulsants cause behavioral or cognitive side effects. Cognitive side effects may be more noticeable in children because of academic emphases and measurable trajectories of cognitive development. Much literature in epilepsy has been devoted to potential side effects of anticonvulsant drugs, and despite the difficulty in isolating etiologies; some medicines have been nevertheless identified as more likely associated with behavioral issues (46).

Behavioral side effects may be reported with any anticonvulsant, but depression and fatigue have commonly been associated with phenobarbital (47). A recent retrospective review suggests that levetiracetam and valproate have behavioral side effects more often than other anticonvulsants, particularly if hyperactivity is noted at baseline (48).

It must also be noted that anticonvulsant drugs often have positive effects upon behavior, particularly in the context of mood disorders, and have proven effective either as primary or adjunct treatments (49). The conundrum of anticonvulsants yielding behavioral or cognitive side effects while at the same time serving as a valuable treatment option is still present.

Childhood Absence Epilepsy (CAE)

Childhood Absence Epilepsy (CAE) is characterized by interruptions in consciousness though with little other visible semiology. Inattention is obvious during the seizures themselves, but also has long been observed in these children in between absence episodes. One study of CAE comorbidity found that 25% had subtle cognitive deficits, 43% linguistic difficulties, and 61% had a psychiatric illness, primarily ADHD (50). Differentiation of CAE from the inattentive subtype of Attention Deficit Hyperactivity Disorder may be difficult (51).

For many years, CAE was considered a benign form of epilepsy, having little sequelae beyond the distraction associated with the discrete events. However, if this were the case, then comorbidities of attention or executive function deficits would not be markedly overrepresented as compared to the typical pediatric population. Instead, the cognitive deficits associated with CAE may be similar to those associated with Attention Deficit Hyperactivity Disorder in children without epilepsy (52). CAE has increasingly become viewed as a disease with persisting cognitive problems, well beyond the time scale of individual absence episodes (53).

The idea that attention and cognitive problems are so prominent in CAE suggests physiologic overlap of cognition and the mechanisms that underlie absence seizures. An intriguing study recently done with fMRI suggests that connectivity in attention, salience, and default mode networks, are altered in CAE (54). The consideration is that these network abnormalities persist beyond discrete seizure episodes and may explain the problems of executive function commonly seen in CAE. Network abnormalities in epilepsy as well as in psychiatric disorders in general may explain a great deal of the overlap, not only with CAE, but with other epilepsies as well. CAE is not just associated with attention or cognitive problems, but may involve mood complications as well (55). The widespread networks subsuming generalized epilepsy may intuitively explain comorbidities present, even in a pediatric population (56).

Mood disorder and Anxiety

Mood disorder and anxiety often co-occur in children and adolescents without epilepsy. Co-occurrence of mood and anxiety disorders and epilepsy is likely to be as common in pediatrics as it is in adults, although large scale prospective studies addressing this comorbidity have not been done (57). Some studies in selected populations suggest co-occurrences of 5-40%, though samples are heterogeneous and assessment tools are variable (58-61). Depression is underreported in pediatrics in

general, and the same may be true in pediatric epilepsy (62, 63). Many with depressive symptoms do not seek mental health treatment for reasons of stigma or lack of clinician availability (64). Clinically, quality of life measures have highlighted the adverse effect of depression in pediatric epilepsy. Similar to adults, the presence of depression has a marked effect upon quality of life and upon recovery post-surgery (65, 66).

The association of depression or anxiety with specific seizure types or localization is less well established. However, two small studies suggest that depression is more often present in children with temporal lobe seizure localization (67, 68). This finding is consistent with literature associating depressive phenomena with temporal lobe pathology in persons without epilepsy (69).

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD has proven to be very common in children with epilepsy. Reports estimate that 30% of children with epilepsy may meet criteria for ADHD, with some reports suggesting prevalence up to 80% (70-72). Both epilepsy and ADHD have problematic effects upon quality of life. A recent report suggests that each condition is significantly detrimental to quality of life, and in combination, the adverse effects upon quality of life may be additive (73).

It is still unclear as to which epilepsy characteristics are related to the presence of ADHD. One preliminary report suggests that attention problems are more common with localization related epilepsy than with primary generalized epilepsy, but the sample was somewhat skewed and psychiatric diagnoses were not obtained at baseline (74). Another study found that 80% of children with frontal lobe sustained abnormal discharges on EEG also met criteria for ADHD (75).

Several reports suggest that EEG abnormalities may be present in children with ADHD even without confirmed epilepsy (76, 77). One report found that treatment with valproate improved

paroxysmal EEG abnormalities as well as ADHD ratings (78). The overlap may not be coincidental as a recent population study suggests that a bidirectional relationship is present between the two conditions. The presence of either ADHD or epilepsy increased the odds for the subsequent development of the other condition (79).

Autism Spectrum Disorders

The overlap between epilepsy and intellectual and developmental disabilities has been frequently reported. Epilepsy may be present in half of children and adolescents with autism or other developmental disorders (80). Family studies also show overrepresentations of EEG abnormalities in persons with family histories of both autism and epilepsy (81). Autism spectrum disorders are characterized by atypical communication, deficits in social reciprocity and stereotyped or narrow ranges of behaviors or activities. Some epilepsy syndromes such as Landau Kleffner Syndrome, include irregular communication styles or atypical social pragmatic language, similar to what is present in autism (82).

Ultimately the overlap may be physiologic in nature. Some evidence suggests that neuronal hyperexcitability may be present in autism spectrum disorders. Epileptiform abnormalities have been reported in autism, in the absence of clinically evident seizures (83). Such neuronal hyperexcitability would be expected in seizure disorders and its presence in autism could reflect common pathophysiology between the two conditions. One study suggests that a deficit in interneurons mediating the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) may be at fault in autism (84). Such deficits in inhibition would be intuitive in epilepsy, which is in one sense, a disorder involving dysregulated neurons that activate inappropriately (85).

Conclusion

The weight of the evidence, regardless of heterogeneity in sampling or disagreements about ideal assessment techniques, clearly affirms that psychiatric comorbidity is a significant problem. Details about bidirectionality, etiology or the possible existence of common pathophysiology are important, but the most important aspect may be the fact that these debates exist at all. The discourse itself results in part from the still underappreciated notion that psychiatric conditions are associated with epilepsy more often than expected.

Ultimately, medical care and treatment decisions relate to quality of life. Quality of life may necessitate bold approaches to treatment. Neurologists are the key directors of epilepsy care and as such, have no choice but to become competent in knowledge of psychiatry. For persons with epilepsy, psychiatric comorbidity appears to be the rule rather than the exception, and as such, comprehensive care demands attention to mental health.

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