The Differential Diagnosis of Anxiety in Individuals With Epilepsy and Intellectual Disability

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Anxiety is the result of a complex interaction between environmental stimuli and a network of brain regions devoted to assessing and responding to threat, conflict, or potential danger. Focal seizures may present with a range of affective symptoms that may be difficult to distinguish from anxiety states. The process is complicated further among individuals with intellectual disabilities. In uncertain cases, clinicians need to consider not only the type of anxiety, but also the nature and duration of symptoms, associated neurocognitive changes, previous treatment response, and in some circumstances, more invasive neurodiagnostic procedures.

Keywords: anxiety, anxiety disorder, developmental disability, differential diagnosis, intellectual disability, mental retardation, psychiatric disorder, seizures

Although it seems counter-intuitive, differentiating anxiety from seizure activity can be a source of considerable uncertainty. In some clinical circumstances, accurate differential diagnosis may require extensive neuro-diagnostic studies—video-monitoring or telemetry EEG, MRI, PET and magneto-encephalography.²⁸,²⁹,³⁴ In people with intellectual disabilities this task is further complicated by developmental deficits in adaptive skills,¹⁹,²¹,³¹,⁴⁰ factors associated with limited social skills,²⁵ difficulties with communication and self-reporting of symptoms,¹⁶,²³,²⁷,³⁷,³⁸ and limited access to these sophisticated neuro-diagnostic procedures. This paper explores these issues in people with intellectual disability (ID).

Normal and Symptomatic Anxiety

Anxiety is a complex emotional state characterized by fear, dread, anticipation of negative events, or potential threat.¹⁰ As a result anxiety can emerge in the context of potential physical danger, excessive novelty or lack of familiarity, past experiences with similar situations or interpersonal threats or conflicts. From this perspective, anxiety has obvious survival value for our species. Because of the importance of anxiety from an evolutionary perspective, it is not surprising that there is a great deal of functional redundancy built into the neurological systems devoted to memory storage (past experiences or fear conditioning), assessment of threat and potential danger, and mobilization of a wide range of behavioral responses.⁸,¹⁴,¹⁵,³³,³⁹ Integrating these complex networks requires the coordination of multiple brain regions (coherence) committed to assessing threat; alerting and orienting responses, and selecting adaptive responses to match the situation.⁹,¹¹,⁴²

This regulatory system also has access to memories (past experiences) and previously successful behavioral strategies. In addition to accessing memories, an effective regulatory system can switch off or override pre-potential motor or previous conditioned responses. This aspect of “top-down” regulation enhances our capacity to adapt to ever-changing environmental circumstances or task demands. “Top-down” regulation of the limbic circuitry can also permit re-appraisal of misperceived threat, and interrupt unwarranted activation of hypothalamic flight or fight responses.¹⁴,²⁰,⁴² The prefrontal cortex plays a key role in this process and provides a top-down regulation of anxiety-driven responses.¹¹,¹⁴,¹⁹,²¹

Anxiety disorders are classified based on clinical phenomenology, severity, genetic loading, age of onset, and neuropsychiatric comorbidity.²²,³²,³⁹ Subtypes of anxiety disorders include social and generalized anxiety, obsessive compulsive disorder, panic disorder with/without agoraphobia, and others. Although anxiety disorders represent considerable heterogeneity, there is sufficient neurobiological evidence to support the presence of specific but overlapping CNS substrates for subtypes of anxiety disorders.⁴,⁸,²²,³⁹,⁴⁰ Many forms of pathological anxiety are related to dysfunction or hyper-reactivity in fronto-limbic circuits.⁴,⁶ Destruction of these anxiety circuits may lead to fearlessness, hyper-exploratory behavior, behavioral disinhibition, and a failure to learn from these negative consequences or danger situations.⁸,¹⁸
Seizure Disorders and Epilepsy

Seizures are paroxysmal electrophysiological events associated with observable changes in mental status or behavior. Seizures (tonic-clonic, partial, absence, myoclonic, etc.) are classified based on semiology (phenomenology of observed changes), EEG signature, and neurological comorbidity. Epilepsy is a brain disease in which seizures are the primary symptom. In general, epilepsy is defined by recurring seizures but no clearly definable etiology, although recent advances in the neurosciences are expanding the list of known etiologies.

Epidemiological studies suggest that the prevalence rates for epilepsy vary across the spectrum of ID. People with severe ID have significantly higher prevalence rates as well as more complicated seizure disorders—increased presence of genetic, metabolic disorders, and structural brain abnormalities. As a result, treatment may require multiple antiepileptic drugs (AEDs). In many situations, the seizures are refractory to medical treatment, and prompt clinicians to try alternative strategies such as vagal nerve stimulation.

Epilepsy and Psychopathology

Seizures differ in terms of etiology and anatomical distribution of electrophysiological abnormalities. The vulnerability to neuropsychiatric symptoms is also sensitive to these factors, as well as age of onset and duration of seizure activity, effectiveness of AED treatment, associated neuropathology, and genetic risk for comorbid psychiatric disorders. Difficult to control seizures increase the risk for cognitive and behavioral disorders probably as the result of adverse effects on neuronal function associated with repetitive seizure activity, high doses of multiple AEDs, and interaction between these factors and underlying metabolic disorders or brain malformations.

Focal seizures may be associated with a wide range of psychiatric symptoms. These cognitive, emotional or experiential phenomena may involve Simple Partial Seizures (without changes in level of consciousness) or present as an aura preceding complex partial (CPS) or tonic-clonic generalized seizures (TCGS). Even though changes in level of consciousness are characteristic of CPS, these ictal changes may be subtle and difficult to recognize. Because many CPS involve the limbic system, it is also not surprising that they are associated with the highest rates of psychiatric symptoms.

Seizure and the Substrates for Anxiety Disorders

Anxiety is a ubiquitous experience for humans. From a developmental perspective, pathological anxiety is a positive symptom that results from a disturbance in several brain regions that normally integrate hierarchically organized functional systems. Anxiety is the result of arousal, neuro-endocrine activation, and perception of threat; lack of readily available solutions or escape routes, conflict situations that give rise to ritualistic responses; and perceived threat. Behavioral inhibition or lowered threshold for avoidance behaviors may be a temperamental manifestation of an overactive fear-anxiety substrate. Differentiating rapidly fluctuating affective states from prodromal, ictal, post-ictal or inter-ictal seizure-related phenomena also poses a significant challenge. Prodromal affective changes may precede the clinical seizure by up to 48 hours. Ictal anxiety or experiential states generally follow the same “rules” as other seizures—abrupt onset of brief, intrusive experiences that are stereotypic in nature, and except for simple partial seizures, post-ictal changes. Post-ictal and inter-ictal anxiety states disorders pose another set of problems. Post-ictal mood changes may be associated with altered sensorium (delirium-like) or emerge abruptly following a lucid period (clear sensorium). Inter-ictal anxiety may be the result of brain changes (regional inhibition) that suppress seizure activity (for example post-ictal paralysis) while affecting sensitivity to environmental triggers or expression of anxiety responses.

Differentiating a Seizure from Anxiety

Focal seizures arising from key limbic structures illustrate the difficulty in distinguishing functional anxiety from seizure-related affective or experiential symptoms. In addition to these ictal anxiety states, affective changes may also occur prodromally (build up to a seizure), post-ictally and inter-ictally. It is important to determine the timing of the anxiety symptoms in relation to seizure activity. In many clinical settings, astute staff may connect affective changes to seizure activity. More commonly, the seizure is missed and staff report post-ictal or inter-ictal anxiety states.
Unfortunately, misattributing other paroxysmal behaviors to seizure activity is also common.\textsuperscript{34,35} Under these circumstances, making a reasonable diagnosis, the clinician needs a good working knowledge of the subtypes of anxiety and seizure disorders. It is also helpful to obtain information about family history, past medical and developmental history, a good description or video recording, as well as an attempt to define a time line or temporal profile for the anxiety symptoms. Time line information includes pattern of onset, duration of anxiety event, associated neurological symptoms, post-event cognitive changes, and relationship of anxiety symptoms to documented seizure activity. This information can be used to rule out other paroxysmal events such as cardiac arrhythmias, migraines, TIAs, syncope and other time-limited behavioral events.\textsuperscript{30}

In many situations, the differential diagnosis and neuropsychiatric work-up is short-circuited in individuals with severe intellectual disabilities. There is a greater likelihood that nonepileptic paroxysmal events will be misdiagnosed as seizures, and unfortunately, treated with antiepileptic drugs (AEDs). Seizures with affective symptoms are also frequently misattributed to reactions to environmental events or primary psychiatric symptoms. Diagnostic overshadowing can emerge from either misinterpretation.\textsuperscript{13,29,41}

Differentiating seizure-related anxiety from primary anxiety disorders also requires careful neuropsychiatric detective work. Several clues may help this process. For example, seizure-related anxiety may be associated with several atypical features—unusual age of onset, lack of genetic risk, previous episodes, and unusual clinical or treatment course.\textsuperscript{30} Resistance to standard treatments for anxiety disorders may also suggest anxiety secondary to possible neurophysiological causes. Aggressive treatment of a misdiagnosed primary anxiety disorder may result in worsening symptoms due to drug effects on seizure threshold; adverse drug-drug interactions; or enhanced sensitivity to unusual or unanticipated sensitivities because of underlying brain dysfunction.\textsuperscript{13,34}

The misattribution of nonepileptic paroxysmal events as seizure activity is also problematic. Anxiety-related symptoms or intrusive events in psychological trauma-related symptoms are examples. In many situations, panic attacks,\textsuperscript{3,30,34,41} flashbacks, and dissociative events are mistaken for seizures.\textsuperscript{2,32} Because of this overlap, a substantial minority of referrals for neurosurgical treatment of medically refractory seizures involve individuals with anxiety-related symptoms—\textit{deja vu}, \textit{derealization}, depersonalization, or dissociative states.\textsuperscript{7,35} This confusion is compounded when studies of functional neuro-imaging and electrophysiological studies also note overlap between symptoms of PTSD and panic disorder and ictal fear arising from the nondominant mesial temporal regions (amygdala and hippocampus).\textsuperscript{2,8,9,14}

Pseudoseizures or nonepileptic seizures (NES) are often equally vexing. The clinical recognition of NESs is frequently complicated by co-existing electrophysiological seizures, developmental disability, and trauma and mood disorders. In order to differentiate seizures from NES, a comprehensive workup may require video/EEG telemetry or more invasive neuro-diagnostic procedures. Since many people with NES also have ID, there can be significant limitations in the process of differential diagnosis—deficits in communication skills, cognitive disorganization, and difficulties self-reporting subjective affective states.\textsuperscript{24,25,37,38} For a variety of reasons, these sophisticated diagnostic procedures are either unavailable or inaccessible for people with severe IDs.\textsuperscript{7,17}

**CASE REPORT**

This case history illustrates the complexity of distinguishing the experience of anxiety from a CPS with fear as a primary symptom. The problem is compounded in this young person by the presence of both panic-like events and a seizure disorder. Other individuals may present episodes of dissociation, derealization/depersonalization, dysphoria or other transient periods of confusion, agitation, or post-ictal delirium.

Mr. K was a 20-year-old white male, who at age 8 secondary developed separation anxiety characterized by intense fear, increased motor activity, clinging behaviors to both parents, and multiple attempts to run home from his classroom. These behaviors were not present during kindergarten, and were unrelated to illness, significant psychosocial stressors, or documented traumatization. At that time, Mr. K met criteria for separation anxiety disorder, but with many features of early onset panic disorder.

Mr. K was diagnosed with mild-moderate ID, and phonological and mixed language delays at age 7. There was no family history of anxiety disorder, ID, neurogenetic disorders, or developmental language disorders. Pregnancy,
labor and delivery and early postnatal course were unremarkable. The was a history of three febrile seizures but only one was greater than one minute in duration.

Temperamentally, Mr. K was described as a shy, retiring child with a slow to adapt style and mild behavioral inhibition. Once comfortable, however, he showed a full range of age (developmental) appropriate social interactions. Peer interactions were noteworthy due to his sensitivity to and spontaneous use of prosodic (tone of voice) and nonverbal, context cues.

An audiological examination revealed no significant hearing deficits. Full scale IQ was within the mild-moderate range of ID with a substantial split between performance and verbal IQ.

Mr. K was referred after failing to respond sufficiently to multiple treatments for his anxiety disorder. These interventions included multiple pharmacological trials, systematic desensitization, shaping, modeling, and valiant behavioral programs by his parents. They denied any symptoms suggestive of a comorbid mood disorder.

Mental Status Examination

Mr. K was a shy child with intense eye contact. He displayed short-lived anxious withdrawal initially and during transitions between tasks. Verbal requests for motor tasks produced inconsistent responses, but his performance improved significantly when same task was demonstrated by the examiner—these gains were sustained on repeat examination 30-45 minutes later. There was no evidence of thought disorganization, hallucinations, or delusions. Mr. K initially deferred most verbal responses to questions to his parents, but as his comfort level grew, he became quite talkative and sociable. His neurological examination revealed significant problem with articulation, as well as mild rigidity, difficulty with motor sequencing and choreoathetoid movements bilaterally. There were occasional facial grimaces, but no consistent motor or phonics tics. Attention span was brief, and often he appeared most inattentive to conversation with his parents. He would respond when requests were directed at him.

Given this history and clinical course, several questions emerged.

1. Is this a classic form of separation anxiety? There was no family history of anxiety disorders.

So why did Mr. K only partially respond to well-designed behavioral therapy, SSRIs, TCAs, Clonazepam, and family therapy?

2. Is this a pervasive developmental disorder (PDD) or fragile X syndrome? Diagnostically, PDDs manifest with significant language deficits, social avoidance, ritualization, and intense anxiety in novel settings. In contrast, Mr. K’s level of social interest and interaction seemed inconsistent with PDD or high functioning autism (HFA). In contrast to autistic children, where social and imaginative play are impaired, Mr. K showed a full range of creative activities consistent with his receptive language age. Fragile X syndrome was a definite possibility; however, his parents declined a chromosome study or DNA probe. Mr. K’s 20-year-old sister was subsequently tested via DNA probe, but showed no evidence of a permutational carrier state. There was no biochemical support for thyroid disease, hypoglycemia nor were there signs of mitral valve prolapse. The parents did not use any OTC drugs that might exacerbate anxiety related symptoms—caffeine intake and the use of herbal supplements such as hypericum perforatum (St. John’s Wort).

3. Was there something that had been “missed”? Several clues emerged with subsequent history. There seemed to be two types of anxiety:

- Type one was characterized by abrupt onset and intense separation anxiety associated with fear and clinging behavior. With graduated exposure and desensitization, this type of anxiety waned in the classroom.

- Intense fear and frantic attempts to run in any direction characterized the second type of anxiety. During these episodes, Mr. K would run into furniture, fellow students, or into walls and doors. During these episodes, his attempts to speak were garbled and incoherent. The latter events appeared to increase with the use of low dose tricyclic antidepressants. Dr. K, his father, observed an episode while driving Mr. K to a college football game. Dr. K reported a sudden onset of a fearful expression, followed by frantic attempts to escape from the car. After stopping the car, Dr. K was unable to communicate with his son, and noted that he appeared confused. This period of disorientation lasted about 10 minutes. Afterwards, Mr. K complained of a headache and wanted to “take a nap.”

   The behaviors described by Dr. K suggested a complex partial seizure based on abrupt onset,
highly stereotyped behavior, brevity (about one minute), and post-ictal confusion and lethargy. As a result of these “spells,” a MRI and EEG were obtained. The MRI was within normal limits; but the EEG showed intermittent temporal spikes. No changes in behavior (escape behaviors) were observed during the EEG. Carbamazepine (Tegretol) was initiated and titrated to a serum level of 8.5 mcg/dL. These “spells” were eliminated within six weeks. CBCs, carbamazepine serum levels, thyroid and liver function studies were followed regularly and remained within normal limits. Over the last 12 years, Mr. K also displayed a seasonal variation in his separation anxiety disorder. His anxiety peaked during late winter (usually increasing after Christmas break), and eventually required low doses of clonazepam. By early spring, clonazepam could be discontinued without re-emergence of symptoms. Phototherapy was also discussed as a possible treatment option, but was never implemented.

Mr. K presents with separation anxiety disorder associated with several risk factors for panic disorder and agoraphobia. Behavioral inhibition in childhood has been linked to familial and subsequent onset panic disorder, avoidance behaviors and agoraphobia (REF).5 Language and cognitive deficits may also contribute to increased sensitivity to social interaction and social phobia (REF).31 Several features of this case should raise red flags. He failed to respond to several commonly effective treatments by excellent clinicians. Approximately 5-10% of patients with anxiety disorders fail to respond to standard treatments. When confronted with treatment resistant anxiety disorders, the clinician may need to rethink the diagnosis (REF). In this case, a careful history revealed the two types of anxiety episodes. For Mr. K, CPS presented with initial fear (at onset) and poorly directed running behavior followed by behavioral arrest, automatisms and a change in consciousness.

This case illustrates the complex relationship between CPS and anxiety disorders. Recent PET, MRI, and quantified EEG studies support a degree of overlap between disorders, especially seizures arising in the right temporal region (REF).

**Treatment Issues**

The quality and effectiveness of treatment is closely tied to four basic issues:

1. Is this a primary anxiety disorder? In general, SSRIs and other anti-anxiety agents improve symptoms in over 90% of individuals with anxiety disorders.12,36 On the other hand, anxiety associated with seizure activity may worsen or require combined treatments.30

2. What is the relationship between anxiety and seizures in an individual with established epilepsy? Seizure-related anxiety may occur as prodromal, ictal, post-ictal, and inter-ictal changes. For many, better seizure control reduces anxiety associated with prodromal, ictal, and inter-ictal symptoms. Exceptions occur, especially when ongoing adverse psycho-social/quality of life issues, underlying brain dysfunction associated with catastrophic anxiety (cognitive and behavioral disorganization),2,18 neuroendocrine disorders; or underlying metabolic disorder are present.8,30,35,40

NESs may also contribute to apparent treatment refractoriness. These individuals require a careful review of semiology, neuro-diagnostic testing when available, behavioral analysis, review of risk factors for psychiatric disorders, and psychosocial/quality of life concerns. These individuals may require more extensive multimodal treatment.7,17

3. Are AEDs contributing to the current affective symptoms or perhaps exacerbating symptoms of a comorbid anxiety disorder? The first issue focuses on potential adverse effects of the AED on mood. Phenobarbital and Mysoline may have an adverse effect on affective states and changing AEDs may reduce emotional symptoms and disruptive behaviors.30 Correcting folate deficiencies associated with Dilantin, valproic acid and barbiturates may be related to overlapping anxiety and cognitive changes.30 Correcting hyponatremia, carnitine depletion and addressing hormonal changes and Polycystic Ovary Syndrome may improve clinical anxiety.30

4. Is persistent anxiety related to drug-drug interactions? Some AEDs are potent inducers of drug metabolism, free drug fraction (competitive protein binding), and receptor binding that may impact the safety and effectiveness of anti-anxiety agents. AED polypharmacy contribute to this problem and may force the clinician to pay close attention to changes in the effectiveness of the AED and anti-anxiety agents.26,35,36
Since both anxiety disorders and epilepsy are common clinical conditions, it is likely that both disorders will be encountered in clinical practice. In spite of their frequent co-morbidity, the actual recognition and differential is often a confusing process. One source of confusion centers on differentiating a seizure from symptoms of several forms of pathological anxiety. As a result of this confusion, many people are referred for medically refractory seizures and are inappropriately placed on multiple AEDs. The reverse process may also occur when seizures present with affective or experiential symptoms and are misattributed to anxiety. This misdiagnosis of seizure as anxiety is more likely to occur if the seizure activity increases during times of environmental change or psychosocial stress. It is also not uncommon to see individuals with both seizures and anxiety. In this situation, the challenge of treating both disorders requires a good working knowledge of the management problems for epilepsy and anxiety disorders.

**Summary**


References:


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