

## Epilepsy in Neurodegenerative Disease: A Commentary

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**Case Summary** - We published a case report of a 22-year-old woman who presented to our university hospital with encephalopathy and left hemiparesis of a few weeks duration. She had been diagnosed with SCA 8 (spinocerebellar ataxia type 8) at the age of 4 years. She was reported to have had spells since the age of 12 and these spells were described as spells of staring, lip smacking, hand movements / automatisms and confusion with postictal lethargy lasting 10-30 minutes. Routine EEG studies showed diffuse slowing with right hemispheric slowing and attenuation with occasional right posterior epileptiform discharges. MRI imaging studies showed right hemispheric diffuse edema and hyperintensity suggestive of seizure related effect. She was noted to have her typical spells in the hospital and was started on video EEG testing which showed multiple frequent seizures of bilateral posterior onset manifesting with her typical semiology. She was diagnosed with nonconvulsive status epilepticus and treated with levetiracetam and lacosamide therapy in addition to lorazepam rescue medication at initiation of treatment. She showed significant improvement in mental status with antiepileptic therapy and was discharged to physical rehabilitation. She returned to clinic for follow up a year later and had made a full recovery with mental status back to baseline (with minimal cognitive impairment) and complete resolution of left hemiparesis. She remained seizure free on levetiracetam and lacosamide therapy and her MRI and EEG studies showed resolution of seizure activity and associated damage as well.

Epilepsy represents a common comorbidity in patients worldwide, with a prevalence including about 1-3% of the population [1]. The causes of epilepsy are diverse and include strokes, TBI, tumors and neurodegenerative disease, among others. Neurodegenerative disease associated epilepsy represents a small but significant cohort of patients that often need closer monitoring,

higher acuity of care and chronic surveillance to minimize morbidity, limit mortality and maintain some quality of life, in addition to assisting caregivers and families with patient care and support.

The spectrum of neurodegenerative disease encompasses commonly seen conditions like dementias to other lesser-known entities like ataxias or storage disorders caused by single or multiple genetic defects. While the individual risk of epilepsy in different disorders varies significantly, the probability of epilepsy in a patient with neurodegenerative disease definitely remains elevated. This principle is of value in evaluating patients with degenerative disorders across all age groups, as the potential benefits from early diagnosis and intervention remain high. Younger patients are more likely to achieve better cognitive development and quality of life outcomes with earlier diagnosis and treatment. Older patients are more likely to minimize cognitive deficits and prevent morbidity from falls and injury with better seizure control, in addition to enabling medical and legal assistance for complex decision making in their advanced ages.

The variety of diseases causing neurodegeneration and epilepsy is different across age groups. Genetic disorders are more likely to present in younger patients within the first two to three decades of life. This is not very surprising, given that one-third of the human genome is devoted to synthesizing proteins that directly or indirectly affect the functioning of the nervous system [2]. Such genetic defects produce neuronal damage or neurotransmitter alterations, resulting in electrical imbalances causing epileptic seizures. Older patients are likely to suffer from cerebral damage from degenerative conditions including strokes, vascular dementia, Alzheimer's or Parkinson's diseases or any of the other dementias of old age, in addition to prion disease, all of which are associated with a varying degree of probability of epilepsy.

Epilepsy is commonly noted to occur in children, within the first 1-12 years of age. Hypoxic injuries represent a common cause of seizures in children. Neurodegenerative disease is usually from storage disorders or genetic conditions. Presenting complaints may vary across syndromes, but usually include some combination of developmental delay, regression of milestones, physical or mental impairments and seizures. Seizures may be frank or subclinical in nature, with both types associated with significant cerebral damage and potential loss of function. Age of onset for seizures has varied from days after birth to few years after birth. Semiology of seizures has included subtle manifestations like staring or muscle twitching to dyscognitive semiologies such as staring or automatisms to frank manifestations such as muscle twitches, hand or leg movements and obvious convulsions. Morbidity and mortality from these seizures can result from a variety of causes, such as status epilepticus, injuries, falls or resultant infections. Cognitive deficits from repetitive seizures and associated damage significantly impair academic performance in school, social interactions and quality of life. Delays or mistakes in diagnosis can often lead to misdiagnoses of psychiatric disease or loss of productive years during childhood, thus significantly affecting quality of life for years to come. The incidence of epilepsy in younger patients can vary from 1-3% for conditions like ataxias to 1-13 % for genetic disorders like phenylketonuria to up to 25% or higher in patients with conditions like the neuronal ceroid lipofuscinoses or progressive myoclonic epilepsies or mitochondrial disorders [3-5]. The severity of presentation and pathology is usually directly correlated with the onset and burden of seizures and this finding can be exploited to use seizure analyses as a surrogate marker of disease pathology and progression.

Older patients with neurodegenerative disease commonly have seizures. Seizures are seen in 10-22% of Alzheimer's patients, with some studies reporting up to 64% incidence of seizures across the duration of monitoring [6,7]. Other dementias like Parkinson's or Lewy Body dementia or vascular dementias also report diverse frequencies of seizures in their patients. The pathology of the disease has a cyclical relationship with seizures in many patients, wherein disease pathology causes brain damage, which then produces seizures, which result in worsening brain damage and progression of disease pathology, and more seizures. This process thus forms a vicious cycle. Older patients sustain significant cognitive and functional damage because of these ongoing processes. Semiologies have included convulsions and smaller dyscognitive seizures in addition to twitches or myoclonus. The myoclonus, especially, can represent a prominent sign of certain degenerative processes like prior disease or other dementias with prominent cortical atrophy and may need treatment for relief.

The EEG forms the mainstay of diagnosis for seizures in patients and this is doubly true with the neurodegenerative population. Besides obvious evidence of epileptiform activity, the EEG also provides additional benefit by capturing focal or diffuse slowing suggesting localized or generalized cerebral dysfunction and serving as a marker of brain damage. Such slowing on the EEG provides supplementary information of brain dysfunction in addition to findings seen on imaging studies.

Routine EEGs and video EEG studies have both shown benefits in diagnosing and evaluating patients with neurodegenerative disease for the presence of seizures. Epileptic activity is usually manifested as epileptiform discharges or rarely, with frank seizures, subclinical or otherwise. Most neurodegenerative diseases do not have a specific EEG appearance, but there are some noteworthy exceptions such as neuronal ceroid lipofuscinosis or CJD, which have specific and pathognomonic EEG findings attributed to them. Routine EEGs are more likely to capture interictal epileptiform discharges and show evidence of epileptogenic potential, thus serving as sufficient evidence for the use of antiepileptic therapy in these patients. The probability of capturing seizures on these is much lower though. They do have the benefit of confirming the diagnosis of epilepsy in patients with reported or witnessed seizures or seizure like events by capturing such interictal data, enabling the treating physician to initiate antiepileptic therapy accordingly. Alzheimer's disease patients have been shown to have interictal abnormalities in about 2-10% of patients, which helped confirm the diagnosis of epilepsy with neurodegenerative disease in them [7]. Our case report of the SCA 8 patient with epilepsy showed useful interictal findings on routine EEG as well and forms the basis for the utility of EEG studies in patients with neurodegenerative disease, the focus of this commentary [3]. Seizure diagnosis may also serve as a heralding sign of oncoming neurodegenerative disease, especially in the absence of a definite etiology for the seizures.

Video EEG testing is of paramount importance in diagnosing these patients, especially due to the ability to capture large quantities of EEG data across sleep and wakefulness and the ability to capture stereotypical events to define their etiology. This feature is of great importance, especially since patients with neurodegenerative disease often show psychiatric symptoms and involuntary movements, both of which are often misidentified as epileptic activity and wrongfully treated with seizure medications. Diagnosing epilepsy and confirming its onset and semiology is often of great value, since it enables prompt initiation of therapy and management of cognitive comorbidities as well. Myoclonic activity is frequent in patients with neurodegenerative disease and can also be confirmed with video EEG testing. Our patient

with SCA 8 and epilepsy had stereotypical spells since the age of 12 years, which were thought to be seizures, but never treated for many years. These spells were finally captured on video EEG at the age of 22 years and then confirmed to be seizures. Our patient presented with hemiparesis, which was probably from multiple episodes of nonconvulsive status epilepticus; a complication that could have been avoided, had she been diagnosed and treated with antiepileptic therapy in a timely manner. She was finally diagnosed and treated for her epilepsy, which resulted in significant improvement in her mental status and physical condition as well [3]. Her case should serve to highlight the importance of EEG testing in patients with ongoing neurodegenerative disease, especially those with known stereotypical spells with features suggestive of epilepsy or otherwise.

Delays in diagnosis often result in significant morbidity and mortality as well. Younger patients with subclinical or undiagnosed seizures are likely to suffer cognitive deficits, including learning difficulties or regression, developmental delay, physical or cognitive impairments, language difficulties, visual-spatial problems and other neurological dysfunctions. These are likely to produce difficulties with education, interacting with family or peers, isolation, embarrassment or misdiagnosis as psychiatric disturbances. Such disturbances during adolescent or teenage years can also affect their relationships with family, friends and make it difficult to sustain meaningful social and romantic relationships. The frequent comorbidity of psychiatric disorders results in additional impairment and diagnostic difficulty with regards to their underlying epilepsy as well. Diagnostic delays in the elderly result in progressive and sometimes, sudden, cognitive impairment which can manifest as memory deficits, personality changes or errors of judgement in addition to worsening difficulties with simple activities of daily living like driving or shopping or paying the bills. This can also significantly affect the lives of loved ones, especially partners or dependent children, many of whom may also be old or highly dependent on the patients. Difficulties with medical or legal or financial decision making from cognitive deficits caused by neurodegenerative disease and seizures are numerous and avoiding or minimizing such instances forms an important responsibility for the physician evaluating such patients. There have been numerous reports from legal authorities about financial frauds perpetrated on the elderly due to their impaired cognitive status. Falls, injuries and infections from seizures or seizure related injuries or aspiration of immobility also represent an important morbid outcome group in such patients and early diagnosis can help minimize or prevent many of these events. Early diagnosis would also have high value in cases with rapidly progressive neurodegenerative

disease, like progressive myoclonic epilepsies or prion diseases.

Diagnostic results often provide useful information to enable timely and appropriate treatment. Antiepileptic medications are often used in these patients for seizure therapy, with adjunct benefits including cognitive improvement, mood stabilization and management of depression or personality disorders. Levetiracetam remains the most commonly used seizure medication due to its lack of interactions with other medications, effectiveness for different seizure types, generally good side effect profile and reasonable dosage regimens [8]. Levetiracetam also works well for myoclonus, which makes it a very good agent for use in neurodegenerative disease patients with epilepsy or myoclonus. Mood or personality worsening in some patients represents a small risk from the use of levetiracetam, but this group of patients forms the minority. Lacosamide is another agent that has great utility in such patients, due to its good side effect profile and lack of interactions. Potential to worsen myoclonus, cost and somewhat restricted availability make this option slightly less attractive than levetiracetam, though it still remains an excellent choice of therapy. Valproate is another agent with excellent utility value in this population. Excellent seizure control, effectiveness against all seizure types, efficacy for myoclonus, cost and ease of use with high availability and the existence of an intravenous formulation for emergencies makes this an excellent choice in this patient group. Hepatic interactions or effects represent the only potential roadblock in its use, especially in younger patients with severe neurodegenerative disease, many of whom have underlying hepatic dysfunction from genetic causes already. Older patients with polypharmacy may also have difficulties due to interactions between valproate and other medications via hepatic metabolic pathways. Other antiepileptic medications like carbamazepine have also been used in some patients due to ease of availability and cost, but hepatic interactions and concerns about pre-existing osteopenia have reduced their use in this patient population, especially the elderly [8]. Our patient did quite well with the use of levetiracetam and lacosamide, especially since both medications were administered intravenously at initiation for the treatment of nonconvulsive status epilepticus. She continues to do well on these two medications, reiterating their importance in this patient population [3]. She has not developed myoclonus, as has been reported in other SCA 8 patients, but we expect to see some benefit from antiepileptic therapy in this regard as well. We are also being vigilant to ensure that the lacosamide does not worsen her myoclonus, were it to eventually present itself.

In summary, we believe that our case report of a patient

with SCA 8 and focal epilepsy serves as a useful template and offers guidance in the diagnosis and treatment of patients with neurodegenerative disease and epilepsy. There is significant variation across different disorders with respect to frequency and severity of seizures and other neurological symptoms and deficits, but our case highlights a diverse variety of difficulties encountered with this patient population - namely, diagnostic delays and difficulties, cognitive and neurological deficits, utility of routine and video EEG studies, decision making in regards to use and choice of antiepileptic therapy and recovery and cognitive improvement with therapy and rehab. We posit that timely, detailed and appropriate evaluation and treatment can help improve quality of life and medical care in such patients, many of whom may not be curable or may not return to baseline.

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