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Review

Seizure clusters: A common, understudied and undertreated phenomenon in refractory epilepsy

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ABSTRACT

Epilepsy is widely prevalent globally and has emerged as a well-studied neurological condition in the recent past. Seizure clusters, a type of seizures, and several aspects pertaining to the etiopathogenesis and management of clusters are yet to be elucidated. This review is an attempt to recapitulate the current understanding of seizure clusters based on the research that has been performed on seizure clusters. This article will provide a comprehensive review of various aspects of clusters, and discusses definitions, prevalence, risk factors, impact on quality of life, approved treatment modalities, and recent advances in management.

Epilepsy is a chronic neurological disorder with an estimated prevalence of 1% among adults in the United States [1]. About 1 in 26 Americans suffers from epilepsy during their lifetime, and approximately 150,000 Americans are diagnosed with epilepsy each year [2]. Clusters, also known as acute repetitive seizures (ARS), flurries, or crescendo seizures, are generally described as seizures occurring in close succession in patients with epilepsy. Clusters have a negative impact on the quality of life of the patients experiencing them and are also associated with a wide range of complications. Clusters, when not managed appropriately, may evolve into status epilepticus, a more severe and life-threatening condition [3].

Despite major advances in various aspects of the management of epilepsy, clusters have been understudied. This article reviews several aspects of clusters including definitions, prevalence, risk factors, impact on quality of life, approved treatment modalities, and recent advances in management.

1. Definitions

Clusters lack a uniform clinical definition that is widely accepted. Studies performed on clusters have laid out several definitions, some of which are clinical definitions based on the absolute frequency and duration of seizures, and others are based on statistical evaluations compared with the patient's baseline seizure frequency. A lack of uniform definition makes comparative research and epidemiological studies hard to interpret.

Many of the studies performed on ARS use a time frame of 24 h to define clusters, which is most likely the easiest way for the patient to report. A randomized controlled trial performed to evaluate treatment for ARS defined them as an episode of multiple complex partial or generalized (tonic, clonic, tonic–clonic, atypical absence, or myoclonic) seizures occurring within a 24-hour period in adults or a 12-hour period in children, with a pattern distinguishable from the patient's usual seizure frequency and with onset readily recognizable by a caregiver, such as a parent [4]. Other observational studies have defined clusters as 3 or more seizures occurring in a duration of 24 h on at least one occasion [5] or 2–4 seizures occurring in a duration of 48 h [6].

Other durations such as 12 h, 6 h, and 4 h have also been used to define ARS. An observational study defined clusters as two generalized tonic–clonic or three complex partial seizures within 4 h [7]. An ongoing prospective observational study by our group defines clusters as 2 or more seizures occurring within 6 h; this is based on a time period that would be a reasonable indication for acute rescue treatment, because of the rapid onset of action of benzodiazepines, especially with nasal, buccal, or intramuscular administration. A large randomized study currently in progress, acute rescue therapy in epilepsy with midazolam intranasal spray—1 (ARTEMIS-1), has also used the criterion of 6 h to define clusters.

Some studies have put forward statistical definitions to characterize clusters more precisely. One such definition is based on Poisson distribution, in which ARS are defined as significantly increased seizure occurrence compared with the rate expected from the individual mean

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[8]. Although statistical definitions are appropriate for research and statistics, they are not used frequently in clinical care.

2. Prevalence

The prevalence of clusters reported by different studies performed on cohorts of variable sizes in different patient settings ranges from as low as 3% to as high as 76% of patients with epilepsy. Such high variability in the prevalence can probably be attributed to the lack of uniform definition. Furthermore, the different settings in which the studies are performed, the different patient populations, and the variable methodology used for data collection could account for this variability.

An observational study performed in 2013 on older adult patients (above the age of 60 years) with epilepsy estimated the prevalence of clusters, defined as three or more occurring in a 24-hour period, to be around 32% [9]. A long-term population-based study that followed a group of 120 patients over a period of 37 years determined the prevalence of clusters, defined as three or more seizures in a 24-hour period, to be 22% [5]. A study conducted using daily diary recordings of 141 patients calculated the prevalence of clusters, defined as three or more seizures in a 24-hour period, as 29% [10]. On the other hand, a large cohort study performed in the United Kingdom on approximately 21,000 patients with epilepsy determined the prevalence of clusters, defined as three or more partial or generalized seizures over a time period of 24 h, as only 3% in patients with epilepsy [11], almost certainly an underestimate. Another recent study using large data from an online seizure diary reported prevalence of clusters of 17.5% [12], defining it as an episode of 2 or more seizures occurring during a 24-hour period in the study population.

More studies, preferably prospective and with large sample sizes, should be performed to precisely identify the prevalence of clusters in patients with epilepsy using various definitions. It may be easier to refer to "24-hour clusters" and "6-hour clusters" as the clinically relevant definition which will change depending on the potential interventions being considered, if any.

3. Etiology and risk factors

Despite many major advances in the management of epilepsy during the last century, a precise understanding of the timing of seizures remains unexplained. The etiology of clusters is poorly understood; however, the basic mechanism is postulated to be the failure of termination of the excitable seizure focus or increased excitation of neuronal circuits that cause epilepsy. Clusters can be associated with any type of seizure disorder. The progression to prolonged seizures or status epilepticus is unpredictable [13].

Individual seizures in a seizure cluster may arise from a single primary epileptic focus or from different epileptic foci. The interseizure interval (ISI) is one of the factors that determines the lateralization of epileptic foci. Shorter durations between the individual episodes (ISI < 8 h) were associated with epileptic foci from the same side in patients with bitemporal epilepsy [14]. In another study of patients with bilateral seizure foci, this association between clusters and laterality was found only in patients with extratemporal seizure foci [15]. In terms of long-term seizure outcome and mortality, patients with seizures demonstrating clustering before receiving any seizure treatment have better outcomes than patients who develop clustering after epilepsy treatment is initiated [5].

Several studies were conducted to identify the factors that lead to the occurrence of clusters in patients with epilepsy. Physiological factors such as fever, hormonal changes (predominantly menstrual), sleep deprivation, and stress have been identified by patients as triggers for the occurrence of clusters [12].

Recent head trauma has been found to be associated with clusters irrespective of the type of epilepsy [10]. The same study also found that extratemporal epilepsy is associated with an increased risk of clustering. Another study found that frontal lobe epilepsy was associated with clusters [16]. The association of frontal lobe epilepsy with clustering was also seen in children younger than 7 years of age [17].

An occurrence of higher frequency of seizures has been significantly associated with the development of clusters, including in elderly patients with epilepsy [9]. One study found that the longer the duration of epilepsy, the higher the chance of developing clusters [18], but another more recent study did not find this association [10]. Not surprisingly, overall poor seizure control has been associated with an increased risk of development of clusters [10]. Findings on MRI, including the absence of white matter changes in the elderly [9] and the presence of mesial temporal sclerosis [19], have been associated with an increased risk of clusters (Table 1).

4. Implications of cluster seizures

Cluster seizures adversely affect the patients experiencing them in terms of clinical and socioeconomic outcomes. Clusters after beginning epilepsy treatment are associated with a lower chance of entering long-term seizure remission and are associated with higher mortality in a long-term study of childhood-onset epilepsy [5]. Clusters are also associated with an increased number of emergency room visits [20]. The socioeconomic impact includes reduced productivity owing to loss of work and school days and increased healthcare-related expenses. Apart from the patients themselves, the condition also impacts the family members and other caregivers. The family members must have an accurate understanding of the condition regarding the use of rescue medications and the appropriate measures required to be taken in the event of nonresponding seizures. Educating family members, friends, teachers, babysitters, daycare workers, etc. about how to manage clusters is important but time-consuming.

5. Management of cluster seizures

The management of clusters includes several aspects such as identifying cluster patterns, prompt use of rescue medications, and prevention of complications associated with clusters. In a recent abstract, healthcare-related expenses in patients using rescue medications were found to be significantly lower compared with those in patients who do not use appropriate rescue medications [21].

Benzodiazepines are the mainstay of therapy in the management of clusters. Efficacy against several types of seizures, rapid onset of action, and relative safety has made this class of medications widely used.

Table 1
Risk factors for clusters.

Triggers
Fever/illness
Menses
Sleep deprivation
Stress
Recent head trauma
Type of epilepsy
Extratemporal epilepsy
Frontal lobe epilepsy
Multifocal epilepsy
Seizure characteristics
Higher frequency of seizures
Longer duration of epilepsy
Imaging
Mesial temporal sclerosis on MRI
Lack of white matter changes (older patients)