Myoclonus in Angelman syndrome

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Abstract

Angelman syndrome (AS) is a neurogenetic imprinting disorder caused by loss of the maternally inherited Ube3a gene and is characterized by generalized epilepsy, limited expressive speech, sleep dysfunction, and movement disorders. Myoclonic seizures are often the first seizure type to appear, and myoclonic status, associated with developmental regression, may occur in the first few years of life. Additionally, there have been rare reports of prolonged episodes of myoclonus without electrographic correlate in adults with AS. The medical records of 200 individuals seen in the Angelman Syndrome Clinic at the Massachusetts General Hospital and the Lurie Center for Autism were retrospectively reviewed to identify and characterize myoclonic seizures and episodes of nonepileptic myoclonus. Myoclonic seizures were reported in 14% of individuals with age of onset occurring before 8 years. These are brief events, unless the individual was experiencing myoclonic seizures and episodes of nonepileptic myoclonus. Myoclonic seizures occurred in 40% of individuals over 10 years of age, and prevalence appears to increase with age. These episodes of nonepileptic myoclonus ariseduring puberty or later, with age of onset ranging from 10 to 26 years. These events were captured on 5 video electroencephalographs and had no electrographic correlate. They can last from seconds to hours, always occurring in the hands and spreading to the face and all extremities in some individuals. Episodes of nonepileptic myoclonus have a discrete beginning and end, lacks a postictal period, and are not associated with significant alteration of consciousness or developmental regression. These episodes can be difficult to treat and are often refractory to medication; however, levetiracetam, clobazam, and clonazepam appear to be effective for some individuals. Myoclonic seizures are common in AS, typically occurring in young children and associated with epileptiform changes on electroencephalographs. Prolonged episodes are associated with developmental regression. In contrast, nonepileptic myoclonus typically begins in adolescence or early adulthood and has no electroencephalogram (EEG) correlate, alteration in consciousness, or regression but can significantly impact quality of life.

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1. Introduction

Angelman syndrome (AS) is a neurogenetic disorder caused by loss of the maternally inherited Ube3a gene, which codes for ubiquitin protein ligase E3A [1–3]. Ube3a is imprinted in the brain and expressed in the cerebellum, Purkinje cells, olfactory tracts, and hippocampus [4,5]. The neurologic phenotype includes symptomatic generalized epilepsy, sleep dysfunction, cognitive impairment, absent or limited expressive language, and movement disorders [6].

The movement disorder of AS includes gross and fine motor delays, an ataxic gait, coactivation of agonist-antagonistic muscle groups, tremor, and aberrant tone [7,8]. Limb movements are characterized by a jerky, discontinuous quality and are often quite stereotyped. The natural history of aberrant movement is largely unknown, but the tremor in AS has been reported to increase in severity with age [9]. In addition to the typical tremor and ataxia, Harbord described two adults with AS who developed Parkinsonian symptoms, including cogwheel rigidity and bradykinesia; these symptoms subsequently responded to dopaminergic treatment [10].

The primary seizure semiologies in AS include atypical absence, generalized tonic–clonic, atonic, and myoclonic seizures [11]. Myoclonic seizures are the most common type at first presentation, but individuals often experience multiple seizure types over their lifetime [5,12]. In addition to myoclonic seizures, individuals with AS may develop myoclonic status epilepticus, also described as myoclonic status in non-progressive encephalopathies (MSNE). This epileptic encephalopathy typically occurs in the first years of life and is associated with decreased interaction and cognitive regression. The electroencephalogram (EEG) pattern consists of generalized rhythmic discharges, consistent with status epilepticus [13–19].

Distinct from both myoclonic seizures and myoclonic status epilepticus, prolonged episodes of myoclonus without EEG correlate, also previously described as cortical myoclonus, have been reported in older
individuals with AS [16]. Individuals may experience periodic episodes of prolonged, irregular jerking of typically one or more limbs, which vary in duration and are not associated with significant alterations in consciousness or cognitive regression. Importantly, these episodes do not have an ictal correlate on EEG [16,20–22]. As the population of adults with a confirmed diagnosis of AS continues to increase, so too does the prevalence of these episodes of nonepileptic myoclonus (NEM). The goal of this study was to further characterize episodes of myoclonus, both epileptic and nonepileptic, in a large population of individuals with AS.

2. Materials and methods

A retrospective review of medical records was conducted for the 200 individuals seen in the Angelman Syndrome Clinic at the Massachusetts General Hospital and Lurie Center for Autism from July 2008 through August 2016. Data were collected from new patient consults and follow-up clinical notes written solely by Dr. Ronald Thibert, in addition to the review of neurophysiological diagnostic reports. Study exclusion among individuals was due to the following: for thirteen, because they had a clinical diagnosis of AS; for one, because the genetic workup was incomplete; and for one, because diagnoses for both AS and cerebral palsy due to birth injury were confirmed. This left a cohort of 185 individuals with a genetically confirmed diagnosis of AS and no other etiologies for movement disorders. Age, gender, and genetic subtype were recorded for all individuals. Age is reported per the completion of the data collection in August 2016.

Data collected regarding myoclonic seizures included age of onset, description of events, and effective treatments. One individual was excluded from this component of the study because of insufficient information regarding seizure history. Age of onset was available for 26/27 individuals with myoclonic seizures, duration for 6/27 individuals, and frequency for 16/27 individuals. As clinical history and interictal discharges are sufficient to diagnose epilepsy in Angelman syndrome, video-EEGs were rarely obtained to capture events. Diagnoses of myoclonic seizures were made based on clinical history, with or without observation of the events in clinic or on video, along with interictal generalized spike and wave discharges on routine EEG.

Data collected regarding episodes of NEM included age of onset, frequency, duration, description of events, EEG findings during and between events, and treatments trialed and their effectiveness and side effects. Duration of episodes was available for 29/35 individuals, frequency for 30/35 individuals, treatment for 34/35, and age of onset for 27/35 individuals. Diagnosis of NEM was based on clinical presentation, focusing on preserved consciousness, lack of a postictal period, duration of events, and typical pattern of starting in the hands, at times spreading to the face and lower extremities. The majority of these events were witnessed either in clinic, in the emergency department (ED), or on video, and 11/35 had events captured on prolonged EEG.

Severity of NEM was categorized by frequency and duration of episodes. Frequency was grouped into three time periods: daily — defined as occurring every day, including multiple episodes per day; weekly — defined as occurring less than every day but occurring at least once every week; and sporadic — defined as occurring not every week but at least a few times a year. Duration of the episodes was grouped into 4 categories: seconds — defined as short episodes that, on average, are shorter than 1 min; minutes — defined as episodes that, on average, last 1 min or longer but are shorter than 1 h; greater than one hour — defined as episodes that routinely last greater than 1 h without breaks but are not the majority of the individual’s wakeful hours; and near-constant — defined as episodes that last the majority of the individual’s wakeful hours. Frequency and duration are reported as those that occurred before initiation of effective treatment and were categorized based on the typical episodes that each patient experiences most frequently.

The effectiveness of trialed antiepileptic drugs (AED) was categorized into 4 groups: greater than 90% improvement; between 50% to 90% improvement; less than 50% improvement; and no improvement or having worsened episodes. Any AED that worsened episodes upon initiation were noted in the results.

This study was approved by the institutional review board at the Massachusetts General Hospital.

3. Results

3.1. Demographics

This cohort includes 185 individuals, 102 (55%) male and 83 (45%) female, ages 1 to 44 years, with an average age of 13 years. In our cohort, 121 individuals (65%) had a maternal deletion of chromosome 15q11.2–13.1, 26 (14%) had a Ube3a mutation, 30 (16%) had uniparental disomy (UPD), 6 (3%) had an imprinting center defect, and 2 (1%) had mosaicism.

3.2. Myoclonic seizures

A history of myoclonic seizures was reported in 27 (15%) of the 185 individuals. It was evenly distributed between 15 (55%) males and 12 (44%) females. Twenty individuals (74%) had a deletion, 3 (11%) had UPD, 3 (11%) had a Ube3a mutation, and 1 (4%) had an imprinting center defect. Of these 27 individuals, 21 had myoclonic seizures, 2 had myoclonic absence seizures, 2 had myoclonic–atonic seizures, 1 had myoclonic status in nonprogressive encephalopathies (MSNE), and 1 had both myoclonic and myoclonic absence seizures. Age of onset ranged from less than 1 year to 8 years, with 18 (78%) reporting onset before age 5. Five reported episodes only lasting several seconds, and only one reported constant myoclonic tremor due to myoclonic status. Seven individuals reported daily or nearly daily events, 5 reported sporadic events defined as occurring monthly to yearly, and 4 reported only having myoclonic seizures in the setting of illness. The myoclonic seizures were diagnosed based on clinical history and interictal generalized spike and wave activity on EEG, as video-EEG was rarely needed for diagnosis and treatment of their epilepsy.

3.3. Nonepileptic myoclonus

Of the 185 individuals, NEM was reported in 35 (19%). It was distributed equally between 18 (51%) males and 17 (49%) females with age ranging from 11 to 44 years. Twenty-two (79%) of these individuals had a deletion, 9 (32%) had a Ube3a mutation, 3 (11%) had UPD, and 1 (4%) had an imprinting center defect. The prevalence of these events, as determined at the time of data collection, appears to increase with age, with no affected individuals under 11 years of age in our cohort, 15 (29%) between the ages of 11 and 20 years, 14 (54%) between the ages of 21 and 30 years, 4 (50%) between the ages of 31 and 40, and 2 (100%) over the age of 40 (Fig. 1).

The age of onset for these events ranged from 10 to 26 years. The majority of subjects’ age of onset was between 11 and 20 years. Only
1 individual (4%) had onset of NEM under the age of 11, 19 (70%) between 11 and 20 years of age, 7 (26%) between the ages of 21 and 30 years, and the remaining 8 did not report age of onset (Fig. 2).

The NEM events occurring in individuals under the age of 20 varied in duration, lasting from several seconds to several minutes with the exception of one individual reporting near-constant myoclonus. For the 13 individuals under the age of 20, 8 reported episodes lasting only seconds, 4 reported episodes lasting minutes, and 1 reported near-constant episodes. For the 16 individuals over the age of 20, 7 (44%) experienced events lasting greater than 1 h, 4 experienced events lasting minutes, and the remaining 5 reported episodes lasting only seconds (Fig. 3). Most individuals exhibit these events daily or more days than not, with only 11 individuals (37%) reporting sporadic occurrence. When the cohort was divided by age, a larger proportion of individuals over the age of 20 had daily or weekly NEM as compared with those under 20 years of age (13 (76%) and 6 (50%), respectively) (Fig. 4). The events of NEM, at minimum, always involve the hands and often spread to the extremities, with 11 out of 28 (40%) also reporting involvement of either the arms or both arms and legs. One individual reported the myoclonus spreading to the face only, 3 reported spreading to the face and extremities, and 1 reported spreading throughout the whole body (Fig. 5). All events have a discrete beginning and end, as none of these individuals experienced random jerks throughout the day. Family members witnessing these events reported no postictal confusion, although the events may cause fatigue, and stated that consciousness appeared preserved during the events.

3.4. EEG of nonepileptic myoclonus

Long-term EEG monitoring was performed on eleven individuals with NEM. Three video-EEGs were performed at our institution; they captured multiple episodes of myoclonus, all of which had no EEG correlate. Two other individuals had video-EEGs performed at external institutions, which were reported as capturing several of each individual’s typical myoclonic events, again none with any EEG correlate. Finally, seven individuals had ambulatory EEGs performed, five at external institutions and two at our institution, all capturing events of myoclonus, none with any EEG correlate. The video-EEGs from our institution had no seizures recorded, and the reports from external institutions did not note any seizures captured.

3.5. Treatment of nonepileptic myoclonus

These episodes of NEM can be difficult to treat and are often refractory to medication. Effective treatments for NEM in some subjects from our cohort included clobazam (CLB), levetiracetam (LEV), and clonazepam (CLZ). Of the 35 individuals who have episodes of NEM, 7 had episodes that were mild and/or infrequent enough that treatment has not been initiated, 1 no longer required medication since episodes had become mild over time, and 1 was treated with other antiepileptic drugs for seizures but had not made any changes to control the NEM specifically. For the other 26 individuals, the number of medications trialed ranged from 1 to 8, with an average of 3 medications. Notably, the 3 individuals with only one medication trialed for NEM began their treatments most recently, and their NEM is mild. Of the 35 individuals, 17 (49%) have episodes that are currently well-controlled but still occur, and 18 (51%) have episodes that continue to interfere with functioning.

The most commonly used and most widely effective medications in our cohort include LEV, CLB, and CLZ, as well as lorzepam (LZP) and diazepam (DZP) as needed. Nineteen individuals were treated with LEV, 6 of whom (32%) reported >90% improvement, 10 (53%) reported 50–90% improvement, and 3 (16%) reported <50% improvement. One individual experienced worsening of episodes on generic levetiracetam, which improved to >90% improvement upon switching to brand name Keppra (this individual is included in the 6 individuals who experienced >90% improvement). Behavior problems were reported in 6 individuals, one of whom showed some improvement over time and another who was affected only at high doses. Generic levetiracetam, as compared with brand name Keppra, was associated with aggression in one individual.

Thirteen individuals were treated with CLB, 4 of whom (31%) reported >90% improvement, 5 (38%) reported 50–90% improvement, and 2 (15%) reported <50% improvement. Efficacy could not be determined for 2 individuals as the medication was discontinued quickly, one due to severe fatigue and another due to agitation. Sedation was reported by 4 individuals, with 3 discontinuing treatment and one affected only at higher doses.
Fourteen individuals were treated with CLZ, 1 of whom (7%) reported >90% improvement, 8 (57%) reported 50–90% improvement, and 5 (36%) reported <50% improvement. Fatigue and increased difficulty ambulating were reported in one of these individuals.

Benzodiazepines taken as needed at the start of myoclonic episodes were typically effective; three individuals showed improvement with lorazepam and four showed improvement with diazepam. One of these individuals also had a significant improvement of events with a daily dose of lorazepam, but this treatment could not be sustained in the long term.

Four other medications were used to treat NEM less frequently with varying efficacy. Of the 12 individuals who trialed valproic acid, 7 reported <50% improvement, but most individuals discontinued this medication because of adverse effects. Of the 8 individuals who trialed lamotrigine, 1 reported <50% improvement and 7 reported no improvement in events. Of the 4 individuals who trialed zonisamide, 1 reported <50% improvement and 3 reported no improvement. Fatigue was reported as a side effect in one individual treated with zonisamide. Finally, of the 3 individuals who trialed rufinamide, 1 reported <50% improvement, and 2 reported no improvement. Side effects reported for rufinamide included lethargy in one individual and gastrointestinal symptoms, which led to discontinuation of treatment in another individual.

Finally, 5 individuals used dietary therapy for these events. Four had an initial but temporary improvement of myoclonus, one with the ketogenic diet and three with the low glycemic index treatment (LGIT). One individual saw mild sustained improvement on the ketogenic diet.

4. Discussion

As the first generation of children diagnosed with AS now enters adulthood, there are increasing reports of prolonged episodes of shaking, clinically consistent with myoclonus. These episodes, although clinically similar to myoclonic seizures in their semiology, vary in their presentation from the myoclonic seizures observed in childhood. Myoclonic seizures are common in young children with AS (typically beginning around age 2–3) and occur in 12 to 50% of children in the total AS population [11,22,23]. Similarly, 14% of our cohort has been diagnosed with myoclonic seizures, and the age of onset in our cohort ranged from less than 1 year to 8 years of age, with the majority reporting onset by age 5. Myoclonic seizures have a short duration, typically lasting several seconds and occasionally up to 1 min.

In contrast, episodes of NEM can last from seconds to hours and have a much later onset, beginning in either adolescence or early adulthood. In the 27 individuals for whom age of onset was available, it ranged from 10 to 26 years, with the majority reporting onset between the ages of 11 and 20 years. Unlike myoclonic seizures or episodes of myoclonic status, these prolonged episodes of myoclonus are associated with no significant alteration of consciousness, regression of skills, or postictal period. During NEM events, the hands always appear to be affected, and the myoclonus often spreads to the upper and/or lower extremities and, occasionally, the face.

Both epileptic and nonepileptic myoclonuses appear to affect individuals with AS across all genetic subtypes. Three of our individuals have a history of myoclonic seizures and currently experience NEM, and there appears to be no correlation between the presence of myoclonic seizures in childhood and occurrence of NEM later in life.

To date, there is little information in the literature with regard to episodes of prolonged shaking in adolescents and adults with AS. Cortical myoclonus was first reported by Guerrini et al. in a cohort of 11 individuals ages 3–28 years [16]. Interestingly, onset of cortical myoclonus is reported as ranging from 8 months to 12 years, which differs from our finding of onset occurring from age 10 to 26 years. Similar to our study, however, EEG monitoring showed no epileptiform activity during episodes of myoclonus. Guerrini et al. used a method of back averaging to determine that the myoclonus was cortical myoclonus.

This methodology was not available to us on routine testing so we can only determine that it was nonepileptic; we are not able to determine with certainty whether the myoclonus is cortical, though that is likely the case. More recently, Goto et al. reported cortical myoclonus in 4 individuals, ages 3–38 years, with UBE3A mutations [24]. The two older individuals, ages 15 and 38, were reported to have longer episodes of myoclonus, ranging from 10 to 15 min in one individual and up to 3 or 4 h in the other individual. Episodes were associated with a change in EEG background activity in one individual, although not epileptic. The other subject’s episodes were sometimes associated with a nonepileptiform EEG correlate but at other times were associated with no changes in EEG. Although our study did not reveal an EEG correlate among our participants, the myoclonic episodes of two individuals in the Goto et al. study appear most consistent with the 35 individuals with NEM in our study.

Severity of NEM varies widely; however, it appears that as individuals age, NEM does not have the tendency to worsen in terms of frequency, duration, and number of areas of the body affected. In six of our subjects, treatment was not started or was not considered necessary. Those that did elect to treat these episodes of NEM, however, found out that these episodes were difficult to treat and were often refractory to medication. The 28 individuals who initiated treatment tried between 1 and 8 medications, with an average of 3 previously trialed medications. Episodes were well-controlled in only 13 of these 28 individuals (46%). Overall, the treatments we have found to be most effective in our cohort were LEV, CLB, and CLZ. Additionally, lorazepam and diazepam, taken as needed at the start of episodes, were reported to be effective in ameliorating NEM in all individuals who took them, though not for every episode. All of these medications were generally well-tolerated, although fatigue was reported with both CLB and CLZ treatment. Behavioral side effects were reported with LEV; however, improvement was noted over time with dose changes or from switching to brand name Keppra. In another study of cortical myoclonus, LEV was effective in 2 of the 3 individuals who initiated treatment [24]. In our study, other medications used with variable effectiveness include valproic acid, laconamide, zonisamide, lamotrigine, and rufinamide, but none of these medications were especially effective.

In addition to medication, one individual initiated the ketogenic diet, and three began the LGIT; all reported some improvement at the start of treatment but efficacy appeared to be transient for all but one individual. With such a small cohort and short duration of treatment, it is difficult to adequately determine the efficacy of dietary therapy for NEM. The most effective medications for NEM appear to be those used most often for the treatment of myoclonic seizures, especially LEV and benzodiazepines, though none of these medications have high rates of efficacy. Brivaracetam has recently become available and may have benefits similar to levetiracetam, but this had not been available long enough to gather any data for this manuscript.

The etiology of these prolonged episodes of myoclonus, although apparently nonepileptic, remains unknown. It is unclear as to whether they are a component of the movement disorder associated with AS or if NEM is a degenerative symptom which worsens over time. Although episodes appear overall to be milder and shorter in duration in the younger individuals, our cohort is too small to infer whether myoclonus worsens over time, particularly in the absence of treatment, or if it remains stable with some individuals experiencing more severe events than others. Similarly, treatment appears to alleviate symptoms, yet future studies are needed to determine if treatment affects the overall progression of myoclonus. The 2 subjects over age 40 both have NEM but no clear regression or loss of skills. This is a very small sample size but the lack of regression is encouraging.

Several confounding factors are inherent in this study. All individuals were seen at a tertiary care center for epilepsy and AS. Therefore, it is likely that the individuals who present to our clinic may have more severe phenotypes. Thus, NEM may be more common than our results indicate and may be milder overall with many individuals experiencing no change in clinical phenotype.
milder events that do not interfere with daily living and for which they have not sought treatment. Additionally, these episodes appear similar to seizures and are frequently characterized as such, especially if there is no EEG performed during the events, again leading to underreporting. Additionally, since these data were collected through clinical care, there was no video-EEG confirmation for the myoclonic seizures, though there were interictal abnormalities, and NEM was captured on prolonged EEG in only 11/35 subjects. We, therefore, relied on clinical presentation and interictal EEG findings for diagnoses for all of the myoclonic seizures and the majority of the NEM. Future prospective studies are needed to further characterize the presentation and natural history of these episodes of NEM.

5. Conclusion

As the number of adults with genetically confirmed AS increases, we are seeing more and more individuals presenting with prolonged episodes of myoclonus, which appear to become more prevalent with age. These events have a discrete beginning and end and can last for hours at a time with preserved consciousness and no clear postictal period. For those who have had these events captured during video-EEG monitoring, there has been no EEG correlate, indicating that these events are nonepileptic and likely part of the movement disorder associated with AS, which also includes tremor and ataxia. These differ from myoclonic seizures in terms of their duration, level of consciousness, age of onset, and EEG correlation. These events can be refractory to treatment, but LEV and benzodiazepines, including CLB, have been helpful for some individuals. Larger, prospective studies are needed to further characterize these events and assess potential treatments.

Conflict of interest

There is no conflict of interest.

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References