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Seizure treatment in Angelman syndrome: A case series from the Angelman Syndrome Clinic at Massachusetts General Hospital

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ABSTRACT

Epilepsy is a common feature of Angelman syndrome (~80–90%), with the most common seizure types including myoclonic, atonic, atypical absence, focal, and generalized tonic–clonic. Seizure types are similar among the various genetic subtypes, but epilepsy in those with maternal deletions is more frequent and more refractory to medication. Treatment with older antiepileptic drugs such as valproic acid and clonazepam is effective, but these medications tend to have less favorable side effect profiles in Angelman syndrome compared with those in newer medications. This study aimed to assess the use of newer antiepileptic drug therapies in individuals with Angelman syndrome followed at the Angelman Syndrome Clinic at the Massachusetts General Hospital. Many of the subjects in this study were on valproic acid therapy prior to their initial evaluation and exhibited increased tremor, decreased balance, and/or regression of motor skills, which resolved after tapering off of this medication. Newer antiepileptic drugs such as levetiracetam, lamotrigine, and clobazam, and to a lesser extent topiramate, appeared to be as effective – if not more so – as valproic acid and clonazepam while offering more favorable side effect profiles. The low glycemic index treatment also provided effective seizure control with minimal side effects. The majority of subjects remained on combination therapy with levetiracetam, lamotrigine, and clobazam being the most commonly used medications, indicating a changing trend when compared with prior studies.

1. Introduction

First described in 1965, Angelman syndrome (AS) is a genetic disorder that significantly impacts neurological development [1]. Angelman syndrome is characterized by an ataxic gait, delayed development with expressive speech more significantly affected than receptive speech, a happy demeanor, and a high prevalence of epilepsy, with an incidence rate of approximately 1 in 15,000 [2]. The syndrome is caused by the loss of function of the maternally inherited *UBE3A* gene that codes for the ubiquitin protein ligase E3A [3–5]. This deficit can occur through different mechanisms: maternal deletion of chromosome 15q11.2-13.1 (68–75%), mutations in the UBE3A gene (UBE3A: 8–11%), uniparental disomy (UPD: 2–7%), and imprinting center defects (IC: 2–5%) [6,7]. Some diagnoses, however, are made based on clinical findings with no genetic abnormality identified (10–20%) [6,7]. For this group, the majority likely have an Angelman-like syndrome that has not yet been diagnosed [8].

Most individuals with AS (80%–95%) will develop a generalized epilepsy at some point in their lives [7,9–12]. Onset of seizures occurs by the age of 3 in 76% of individuals [11], and seizures typically improve during puberty but can return in adulthood, affecting up to 40% of the population [13]. Seizures can be of different semiologies [10,14,15], and the most common include myoclonic, atypical absence, generalized tonic–clonic, and atonic seizures [7,9,11,16]. Additionally, focal seizures have been reported in 13–39% of individuals with epilepsy [7,16], as well as rare cases of infantile spasms [17]. Different antiepileptic drugs (AEDs) are used to treat seizures in those with AS with varying results. Valproic acid (VPA) and clonazepam (CLZ) are commonly used in AS with reportedly high efficacy [7] and were the only broad spectrum AEDs available prior to the mid-1990s. In a large survey-based study of 461 subjects with AS, family members reported levetiracetam (LEV) and lamotrigine (LTG), and to a lesser extent topiramate (TPM), had similar efficacy rates compared with VPA and CLZ in terms of controlling seizures but with more favorable side effect profiles. Clobazam (CLB) was not yet available in the US at the time of the study, so data were not available. The aim of this study was to assess the effectiveness rates and side effect profiles of these medications in a large cohort of children and adults with AS using medical records from the Angelman Syndrome Clinic at Massachusetts General Hospital (MGH AS Clinic).

2. Methods

We retrospectively examined the medical records of children and adults seen at the MGH AS Clinic from 2008 to 2015. Records were

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reviewed for subjects' genetic subtype, seizures types, seizure treatments including dosages of medications, and response to treatment. Subjects were excluded if they did not have a confirmed genetic diagnosis of AS, had additional genetic abnormalities, were not primarily managed at the MGH AS Clinic, or had frequent nonepileptic myoclonic events that made it difficult to assess their true response to medications. Only data on therapies initiated or managed at our clinic were included in the study to ensure accuracy.

At the time of this study, the MGH AS Clinic had seen 153 individuals with AS. Of these, seven had a clinical diagnosis with no clear molecular subtype, and seven had additional genetic abnormalities. Forty-nine subjects had only been seen once or had their epilepsy primarily managed by neurologists outside the clinic, and five had significant nonepileptic myoclonus. Our cohort was thus reduced to 85 subjects. Some subjects were excluded only from the average dosage calculations of VPA (four), LTG (two), LEV (two), CLB (one), CLZ (one), and TPM (one), as their weights were unavailable. Data were collected from clinic visit notes written by the same physician in the same format, which ensured consistency. In the clinic visit notes, effectiveness and side effects after each AED change were noted. Data on drug effectiveness and side effects were recorded from the subject's first clinic visit through the end of data collection on December 1, 2015. Any history of AEDs that subjects had trialed prior to their initial clinic visit was also collected if prior records were available.

3. Results

Data were obtained from 85 subjects, 56 of whom had a maternal deletion (66%), 14 had UBE3A (16%), 10 had UPD (12%), and 5 had IC (6%). This distribution is representative of the general population with AS and in line with previous reports [7]. Of the 85 subjects, 63 had epilepsy (74%) including four with reported infantile spasms. Epilepsy rates, however, differed among the genetic subtypes with deletion-positive subjects having a higher rate of epilepsy (88%) compared with those with UPD (40%), IC (40%), and UBE3A (57%). Detailed results are shown in Table 1. The cohort was comprised of 48 males and 37 females with an average age of 12.4 years, with the youngest and oldest subjects being 3 and 38 years of age, respectively.

Twenty-five (40%) subjects had a course of VPA with the majority (67%) experiencing a greater than 90% seizure reduction and the rest (33%) experiencing a decrease of at least 50%. Eighteen out of twenty-five (72%), however, experienced adverse effects — mainly increased tremor but also increased ataxia and decline of gross and/or fine motor skills. Only 10 (40%) subjects remained on VPA with only 2 (8%) on VPA monotherapy while the average dose was 26.4 (8.7–60.5) mg/kg/day.

Six (10%) subjects had a course of CLZ with 3 reporting a decrease in seizure frequency greater than 90%. Two (33%) developed adverse effects including sedation, decreased tone, and increased drooling. Two (33%) remained on CLZ therapy with none on CLZ monotherapy while the average dose was 0.04 (.01–0.133) mg/kg/day.

Nine (14%) subjects had a course of TPM with 3 (33%) reporting a decrease in seizure frequency greater than 90% and 4 (44%) reporting a decrease in seizure frequency of at least 50%. One did not tolerate the medication and discontinued it shortly after developing a rash. Four (44%) developed adverse effects including fatigue, irritability, and loss of appetite. Three (33%) remained on TPM therapy with none on TPM monotherapy while the average dose was 7.22 (2.5–10) mg/kg/day.

The majority of subjects (n = 42; 67%) had a course of LEV with excellent effectiveness. Thirty-six of the forty-two subjects (86%) saw a reduction in seizure frequency greater than 90% after LEV was initiated. Adverse effects were noted in 21% of subjects and consisted of behavioral changes with one report of exacerbation of seizures only at higher doses. Thirty-three (79%) remained on LEV with 15 (36%) on LEV monotherapy while the average dose was 56.83 (6.15–210) mg/kg/day.

Eighteen (29%) subjects had a course of LTG, and 16 (89%) had a decrease in seizure frequency greater than 90%. Three (17%) developed adverse effects including OCD-like behavior, tics, and difficulty sleeping. Twelve (67%) remained on LTG, with 5 (28%) on LTG monotherapy while the average dose was 6.32 (2.5–11) mg/kg/day.

Thirty-two (51%) subjects had a course of CLB with 27 (93%) reporting a decrease in seizure frequency greater than 90%. Three (9%) did not tolerate the medication and stopped taking it after the initial few doses, and one developed a rash on his arm and leg. Eleven (34%) reported adverse effects including sluggishness and aggression. Twenty-four (75%) remained on CLB therapy, with 10 (31%) on CLB monotherapy while the average dose was 1 (0.18–2) mg/kg/day. There did not appear to be more frequent dose increases for breakthrough seizures compared with the other AEDs, indicating that tachyphylaxis was not a significant factor in using this medication.

In addition, five or fewer subjects had courses of rufinamide, lacosamide, and/or zonisamide with varying results. Rates of side effects and of those able to be maintained on monotherapy are presented in Fig. 1.

Twelve subjects were placed on low glycemic index treatment (LGIT), and all reported a decrease in seizure frequency while 10 (83%) reported a decrease greater than 90%. Eight remained on LGIT. Detailed results of the effectiveness of all treatments are presented in Table 2.

4. Discussion

Most individuals with AS will develop seizures at a young age. Although seizures are more frequent in those with maternal deletions when compared with the other genetic subtypes, seizure semiology is similar among the subtypes, and differences in responses to the various

Table 1
Subject distribution among genetic subtypes and epilepsy rates.

Genetic diagnosis	With seizures	Without seizures	Total
Deletion	49 (88%)	7 (22%)	56 (66%)
UBE3A	8 (57%)	6 (43%)	14 (16%)
UPD	4(40%)	6 (60%)	10 (12%)
Imp center	2 (40%)	3 (60%)	5 (6%)
Totals:	63 (74%)	22 (26%)	85

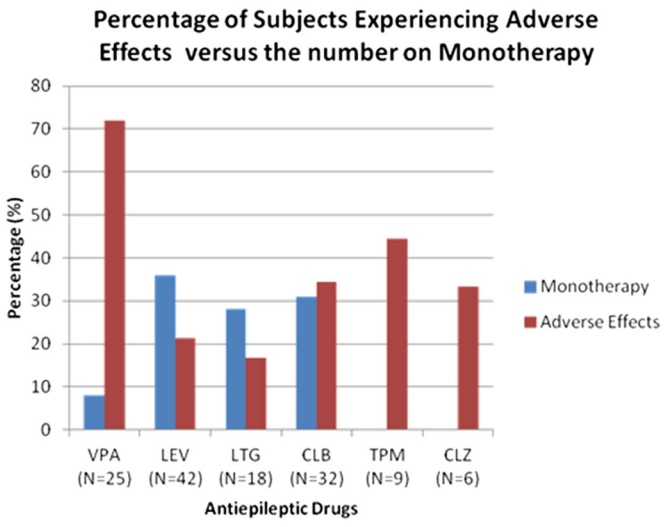

Fig. 1. Percentage of subjects who are continuing a course of monotherapy for each AED (blue) as well as the percentage of subjects who experience adverse events after AED was added either as initial monotherapy or as an add-on medication (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Breakdown of change in seizure frequency for the different treatments.

Treatment	No change	Less than 50%	Between 50 and 90%	Greater than 90%
VPA	0	0	8 (33.3%)	16 (66.7%)
LEV	0	0	5 (14.3%)	36 (87.8%)
LTG	0	0	2 (11.1%)	16 (88.9%)
CLB	2 (7.1%)	0	2 (6.9%)	27 (93.1%)
TPM	0	1 (12.5%)	4(50%)	3(37.5%)
CLZ	0	0	3(50%)	3(50%)
LGIT	0	0	2 (16.7%)	10 (83.3%)

treatments could not accurately be detected because of the small size of our cohort.

Several reports have found valproic acid to be an efficient treatment of seizures in patients with AS [18]. Although our results support VPA as an effective medication for seizures in AS, we found that it also tends to worsen tremor and balance with 72% of our cohort on VPA reported experiencing these types of adverse effects while on the medication, including a more significant decline of gross and/or fine motor skills with some losing the ability to ambulate. Nearly all of the subjects on VPA in our cohort were started on this medication prior to being seen at the clinic. In most cases, they were weaned off VPA because of the increase in tremor and decrease in balance despite adequate seizure control. The change of drug regimen was typically successful in decreasing side effects, and the newer medications to which they were switched had better overall side effect profiles and similar levels of seizure control. A small proportion (8%) of those subjects that trialed VPA remained on monotherapy.

The other older medication that was used very frequently in our survey from 2009 was CLZ [7]. Our results indicate that CLZ was found to have a similar rate of adverse effects compared with CLB (higher than LEV and LTG) with less effectiveness, though it is a very small sample size ($n = 6$). Only one-third of subjects remained on CLZ with none currently on monotherapy, compared with three-fourths of patients remaining on CLB with 31% on monotherapy.

In the survey from 2009, it was found that newer medications such as LEV and LTG, and to a lesser extent TPM, were as effective as VPA and CLZ with fewer side effects. In the current study, TPM was found to be less effective than the other treatments studied (though with a small $n = 9$), with more than half of the subjects taking TPM experiencing less than 90% seizure reduction. In addition, 44% of subjects who had taken TPM experienced adverse effects such as fatigue, irritability, and lack of appetite, which may be at least part of the reason it was less effective than in prior reports. Only one-third of subjects who had a course of TPM were still taking it, none on monotherapy.

Levetiracetam was the best-tolerated drug in our cohort. Twenty-one percent of subjects developed various behavioral problems while taking this medication, and these behaviors subsided once the drug was discontinued. This is in line with previous reports of behavioral side effects of levetiracetam in the general population with epilepsy [19]. Levetiracetam was also highly effective in controlling seizures, with all subjects experiencing a reduction in seizure frequency of at least 50% and 88% of subjects experiencing a decrease greater than 90%. Only 15 (36%) subjects, however, remained on LEV monotherapy while 18 (43%) remained on combination therapy, indicating that LEV may be most effective when added to other AEDs in this population. Lamotrigine had a similar side effect profile to LEV with 17% of subjects experiencing side effects, and it appears to be at least as effective as VPA, if not more so [7]. Sixteen of the 18 (89%) subjects on LTG experienced a decrease in seizure frequency of greater than 90%, but only 5 (28%) were on LTG monotherapy. A case series reports similar effectiveness of LTG in five individuals with AS [20].

Clobazam is another well-tolerated medication that has more recently become available in the United States. Thirty-four percent of subjects on CLB reported experiencing some side effects — mainly drowsiness and, less commonly, agitation. A reported 75% remained on CLB with 31% on CLB monotherapy with no clear adverse effects. Very little has been published about the use of CLB to treat epilepsy in AS, but it has been hypothesized that GABA agonists are increasingly effective in this population given the location of the $GABA_A$ receptor genes in the AS critical region [21,22].

The LGIT appears to be very effective in controlling seizures in those with AS. In our cohort, 9 of the 12 (75%) subjects utilizing the LGIT exhibited a decrease in seizure frequency of 90% or more. Again, in the majority of cases, LGIT was used in combination with one or more AEDs, most commonly CLB. This is supported by a small prospective trial of the LGIT in AS [23]. Six subjects in this cohort were part of that prospective study on LGIT performed in our clinic, and the detailed results were published in 2012 with four of six children showing >90% seizure reduction and one showing a 50–90% reduction [23].

Since our study only reviewed the medications we prescribed and managed, the effectiveness noted in our cohort is likely exaggerated as many of the AEDs prescribed were added on to previously existing AEDs, and these effectiveness rates are higher than previously described [7]. These rates do not represent the exact effectiveness of each medication as monotherapy, as the epilepsy in children with AS is difficult to treat and most children are on multiple AEDs. Rather, they are more representative of how effective they are relative to one another. True studies of effectiveness of various AEDs as monotherapy in AS would need to be done prospectively. Moreover, in all but one of the cases reported, initiation of valproic acid therapy was done prior to their visit to the clinic, as we do not typically prescribe it as a first line treatment because of its side effect profile in AS, so some of these subjects may have had better responses initially. Our results show a changing trend in AED usage in AS. In the survey published in 2009 (with data collected in 2006–7), families (mainly in the US) reported valproic acid as the most commonly prescribed AED (62%) while CLZ (34%) and TPM (30%) were also fairly commonly prescribed, and LTG (24%), LEV (20%), and CLB (4%) were less frequently utilized. This contrasts with our clinic's use of VPA (39.7% but nearly all prescribed prior to the initial clinic visit), CLZ (9.5%), and TPM (14.3%) compared with that of LTG (28.6%), LEV (66.7%), and CLB (50.8%). As this was a retrospective study conducted using only data from our clinic to ensure accuracy, there were some limitations, especially lack of data from prior to the initial visit and the confounding factor of subjects already being on medication when these AEDs were added.

5. Conclusion

In summary, our cohort of 85 individuals with AS shows an epilepsy prevalence of 74%, which is consistent with previous reports in the literature. The prevalence of epilepsy in our cohort may differ from the true prevalence since the Angelman Syndrome Clinic at the Massachusetts General Hospital is run by a pediatric epileptologist and therefore may draw in more subjects who specifically seek treatment for seizures and because the youngest subjects in our cohort simply may not have yet developed seizures. In the large survey published in 2009, newer medications such as LEV and LTG (and to a lesser extent TPM) showed similar effectiveness with fewer side effects compared with older AEDs such as VPA and CLZ. Our results support these findings as both LEV and LTG showed better effectiveness than VPA and CLZ with fewer side effects than CLZ and significantly fewer side effects than VPA. Topiramate was nearly as effective as LEV and LTG in the survey but with higher rates of side effects, and in the current study, the rate of side effects was again notably higher, likely accounting for the lower effectiveness rate. Clobazam was not readily available in the US when the survey was performed, so there was insufficient data on this medication. Our results show CLB to be very effective in this population with a side effect profile similar to CLZ and much more favorable than VPA. In addition, the LGIT remains an effective treatment for seizures in AS with an excellent side effect profile. A large scale multicenter study to assess the effects of newer AEDs and dietary therapy in this

specific population would be needed for more definitive results, especially to accurately assess efficacy of AED as monotherapy.

Conflict of interest

None of the authors have any conflicts of interest to report.

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