Review article

Epilepsy in Angelman syndrome: A scoping review

Debopam Samanta

Child Neurology Section, Department of Pediatrics, University of Arkansas for Medical Sciences, Debopam Samanta 1 Children's Way, Little Rock, AR 72202, USA

Abstract

Angelman Syndrome (AS) is characterized by severe developmental delays including marked speech impairment, movement abnormalities(ataxia, tremor), and unique behaviors such as frequent laughter and is caused by dysfunctional maternal *UBE3A* gene (maternal 15q11-13 deletions, maternal specific *UBE3A* mutation, uniparental disomy, and imprinting defect). Intractable epileptic seizures since early childhood with characteristic EEG abnormalities are present in 80–90% patients with AS. Underlying pathophysiology may involve neocortical and thalamocortical hyperexcitability secondary to severe reduction of GABAergic input, as well as dysfunctional synaptic plasticity, deficient synaptogenesis, and neuronal morphological immaturity. The onset of epilepsy is most prevalent between 1 and 3 years of age; however, approximately 25% of patients developed epilepsy before one year of age. Various types of generalized seizures are most prevalent, with most common types are myoclonic and atypical absence. More than 95% of epilepsy patients may have daily seizures at least for a limited time during early childhood, and two-third patients develop disabling seizures. Fever provoked seizures, and frequent occurrence of nonconvulsive status epilepticus are two unique features. Seizures are frequently pharmacoresistant. Considering underlying prominent GABAergic dysfunction, clinicians had used AEDs that target GABAergic signaling such as valproate, phenobarbital, and clonazepam as first-line therapies for AS. However, due to the unfavorable side effect profile of these AEDs, a recent treatment approach involves priority use of levetiracetam, clobazam, topiramate, lamotrigine, ethosuximide, VNS, and carbohydrate-restricted diets. Besides symptomatic management, there has been recent progress to find a curative treatment with the following approaches: 1. Gene/protein replacement therapy (Adeno and lentiviral vector therapy to deliver a gene or secretory protein); 2. Activation of the intact but silent paternal copy of *UBE3A* (antisense oligonucleotide therapy and artificial transcription factors); and 3. Downstream therapies (OV101/gaboxadol, ketone supplement, novel compounds/peptides, anti-inflammatory/regenerative therapy).
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Keywords: Angelman syndrome; *UBE3A*; Epilepsy; seizures, EEG; Gene therapy; Molecular therapy

1. Introduction

Angelman Syndrome (AS), a severe neurodevelopmental disorder, is caused by the dysfunctional maternal *UBE3A* gene. First described in 1965, the prevalence of AS is estimated as 1 in 12,000–20,000 live births. AS is characterized by severe developmental delays, including marked speech impairment, movement abnormalities (ataxia, tremor), and unique behaviors such as frequent laughter. Intractable epileptic seizures since early childhood with characteristic electroencephalographic(EEG) abnormalities are present in 80–90% patients with AS [1–3]. Although epilepsy phenotype, neurophysiological abnormalities, the relative efficacy of antiepileptic drugs (AEDs), and natural history of epilepsy have been described in detail for a while, a better understanding

of underlying pathogenesis and development of molecular therapeutics with hope towards the development of curative therapy for AS is relatively recent.

2. Pathophysiology

2.1. Genetics

Between chromosome 15 pairs, only maternal *UBE3A* is functionally active in the brain as paternal *UBE3A* undergoes functional silencing by the process of antisense transcription(ATS) [4]. Genomic imprinting occurs in a tissue-specific manner during gametogenesis, and only maternal expression of Ube3a is seen in the brain. Large (5–7 Mb) deletions of 15q11-13- containing critical *UBE3A* gene- in the maternal allele, which occurs in 70% of AS patients, cause deficient production brain-specific Ube3a proteins [5]. These proteins (enzymes) are essential for the ubiquitin-ligase pathway to facilitate protein degradation(by tagging) in the proteasomes. Appropriate expression of Ube3a is also crucial for synaptic plasticity, synaptogenesis, neuronal morphological maturity, and maintenance of proper levels of neurotransmitter gamma-Aminobutyric acid (GABA). Deficient expression of Ube3a protein also occurs secondary to maternal *UBE3A* mutation (approximately 11% of AS patients), uniparental disomy (noted in about 7% of AS patients with both copies of 15q 11–13 inherited from the father and none from the mother), and imprinting defect (rarest known genetic cause of AS and noted in approximately 3% of AS patients).

2.2. GABAergic neurotransmission

Due to characteristic presence of intractable seizures and EEG changes associated with AS, initial research on pathogenesis was focused on GABA(the principal inhibitory neurotransmitter in the cortex) that maintains inhibitory tone in the brain and counterbalances excitatory glutamatergic outputs [6,7]. GABA mediates its action via GABA receptors, which composed of 5 subunits. Commonly deleted region in AS, 15q11-q13, contains genes that codes for different subunits of $GABA_A$ receptors (α 5, β 3, and γ 3) and thus possibly indicate disruption of GABAergic neurotransmission in AS. Knock-out animal models using these GABA receptor genes had been previously utilized in the AS research [8]. Particularly *Gabrb3* knock-out mice expressed some similarities to AS patients with seizures susceptibility and EEG changes [9,10]. However, 30% of AS patients (AS patients without 15q11-13 deletion) do not have *GABARB3* involvement. Additionally, *Gabrb3* knock-out mice do not express all the characteristic features of AS. There is also no evidence of imprinting of *GABARB3* in humans. As all patients with AS have a

deficient function of *UBE3A*, the recent focus of research has shifted to the understanding of pathogenesis-related to the ubiquitin pathway. Although maternal *UBE3A* gene dysfunction is causative for AS, adjacent GABA genes may contribute to the neuronal hyperexcitability and may be responsible for more severe phenotypes associated with the deletion subtype compared to the other three causes of AS. Moreover, recent studies have demonstrated GABAergic dysfunction caused by loss of function of *Ube3a* in a mouse model(detailed in the next section) [11]. The decrement of inhibitory synaptic input to the principal neuron may originate from the defective presynaptic vesicle cycling in multiple interneuron populations. Additionally, *Ube3a* deficient mice might have a surplus of GABA transporter 1 due to a lack of binding of the transporter with Ube3a [12]. This excess level of transporter might induce decreased tonic inhibition by diminishing GABA concentration in the extrasynaptic space.

2.3. Circuit hyperexcitability

Neocortical hyperexcitability in layers 2 and 3 of pyramidal neurons, secondary to severe reduction of GABAergic input, has been established in an AS mouse model specific to *UBE3A* mutation. The reduction of the GABAergic input might be disproportionately affected than the loss of excitatory glutamatergic input, even with the isolated loss of Ube3a expression. In a *Ube3a* mouse model, an increase in the seizure susceptibility was noted with the depletion of Ube3a in GABAergic neurons without any obvious neuronal loss or mossy fiber sprouting. Interestingly, this increased seizure susceptibility was reversed with increased Ube3a expression [13]. The authors also reported that the rescue was successful in juvenile mice (postnatal day 21), but not during adulthood, and speculated that there are "critical periods" for such intervention. However, the treatment windows for the prevention of epilepsy may persist for a longer duration compared to other AS phenotypes such as developmental delay, repetitive behaviors, and anxiety. This relatively longer treatment period may be due to the gradual accumulation of cellular and circuit-level pathologies over a prolonged period of time prior to the emergence of epilepsy. Besides the alteration of neocortical circuits, hyperexcitability has also been postulated secondary to the abnormal oscillatory activity of the thalamic reticular nucleus. Further studies showed an accumulation of clathrin-coated vesicles in presynaptic terminals of the pyramidal neurons to suggest a disruption in the presynaptic recycling, which is critical for synaptic physiology. Neuron-specific studies revealed that specific GABAergic Ube3a deletion produced characteristic delta slowing in the electrophysiological studies as well as an increase in seizure susceptibility [14]. On the contrary, glutamatergic

Ube3a loss decreased tonic GABAergic inhibition without any change in the EEG or seizure susceptibility pattern. However, glutamatergic Ube3a loss may be relevant for other neurologic functions, such as cerebellar granule cells mediated locomotor activities.

3. Epilepsy phenotype

Approximately 80–90% of patients with AS develop epilepsy [15]. The onset of epilepsy is most prevalent between 1 and 3 years of age; however, about 25% of patients develop epilepsy before one year of age [16]. Early-onset of seizures may be strongly associated with autistic symptoms, even after controlling the particular genetic abnormality [17].

The deletion subtype is associated with the most severe epilepsy phenotype, followed by isolated UBE3A mutation [18]. Uniparental disomy subtype is associated with the lowest frequency of epilepsy and exhibits the least severe epilepsy phenotype. Non-deletion patients, in general, may have relatively late-onset seizures. Moncla et al. compared 20 deletion and 20 non-deletion AS patients and noted that all non-deletion patients had rare seizures, and 7/20 patients (age 4–30 years) were seizure-free and several patients successfully stopped seizure medications [19]. In this study, atypical absence and myoclonic seizures were the most prevalent seizure type in the non-deletion cohort, but in contrast to the deletion AS patients, tonic-clonic seizures, infantile spasms, and myoclonic status epilepticus were not reported.

3.1. Seizure types

Both generalized and focal seizures have been reported, but isolated focal seizure is rare. Reflex seizures are also have been described [20,21]. Multiple types of seizures are usually present concurrently. Various types of generalized seizures are most prevalent, and myoclonic seizure is the most common type during infancy. The other two common seizure types are atonic and atypical absence seizures. Approximately 50% may have focal seizures [22]. Fever aggravated seizure is present in 50% of cases. Fever can trigger the 1st seizure, and seizure can be triggered with a modest change in temperature [23]. Although febrile seizure can rarely be the only seizure event, it most commonly follows with other seizure types. More than 95% of epilepsy patients may have daily seizures at least for a limited time during early childhood, and 2/3 patients develop disabling seizures [22,24].

3.2. Status epilepticus

Status epilepticus is particularly common and seen in 35–85% of cases [22,25]. Generalized tonic-clonic seizures can be present, but convulsive status epilepticus is rare. Myoclonic status in nonprogressive disorders has been frequently described in AS when the child presents with continuous/ semi-continuous fragmentary myoclonus (rhythmic or arrhythmic symmetric and asymmetric jerks involving limbs, trunk, and face with or without atypical absence) with altered mental status and drooling [26]. Regression in milestones can be prominent such as an inability to walk or worsening of the gait. This particular type of status is more prevalent in 15q11-13 deletion and *UBE3A* mutation subtypes and less frequently associated with uniparental disomy [26]. Other than typical myoclonic features, nonconvulsive status epilepticus can be manifested as increased seizure activity or cluster of seizure activity at the onset of the episodes in association with some features of the following: Intermittent eye-rolling, eyelid fluttering, head nods, altered mental status, fatigue, sleepiness, developmental regression, and diminished communication. Due to the indistinct nature of many features, heightened suspicion is necessary for prompt diagnosis of these subtle status episodes. Sometimes triggers can be identified, such as infection, recent change or noncompliance with the AED regimen, or worsening sleep dysfunction. EEG shows high voltage, frontally dominant, slow spike-wave discharges comprising 50–95% of the recording. AS patients typically have less frequent episodes of status after puberty.

3.3. Infantile spasms

Several reports of infantile spasm exist in association with EEG findings of hypsarrythmia. However, misclassification is possible due to the presence of pseudo-hypsarrythmia and episodes of nonepileptic or epileptic myoclonus or atonic seizures. This is particularly relevant as first-line AED for infantile spasms such as vigabatrin may worsen myoclonic and/or absence seizures with overall clinical deterioration.

There are few nonepileptic events that can be misclassified as seizures in AS, such as continuous tremors like movement that disappears during sleep, nonepileptic myoclonus (no EEG correlates present), and paroxysmal laughter. The prevalence of nonepileptic myoclonus increases with age. Frequently, myoclonus may involve hands first followed by spreading to the face [27]. These episodes are not associated with alteration of consciousness and typically refractory to treatment.

4. Electroencephalography(EEG)

4.1. Characteristic EEG features

AS patients have characteristic EEG abnormalities, and almost all patients had EEG abnormalities with or without seizures [25,28–31]. Boyd et al. reported EEG in 11 children with clinical features of AS (age range:

11 months-11 years, most individuals were less than 5 years of age) and identified three high-voltage features in isolation or combination: 1. Persistent rhythmic 4–6 Hz, $\geq$ 200 µV activities during wakefulness 2. Prolonged runs of anterior dominant, rhythmic 2–3 Hz (200–500 µV) with or without admixed spike-wave discharges 3. Posterior dominant 3–4 Hz $\geq$ 200 µV notched delta and theta activities (admixed with ill-defined spike-wave) facilitated with eye closure. (Fig. 1). This last finding has been predominantly seen in children less than 12 years old. Vendrame et al. showed an age-dependent decrease in the central-temporal/occipital delta waves with advancing age [32]. EEG abnormalities have been proposed to be used as a reliable biomarker in research studies. Frohlich et al. reported spectral power of clinical EEG recording in AS children and noted an elevated theta power (peak frequency: 5.3 Hz) and diminished beta power (peak frequency: 23 Hz) in the deletion genotype (37 patients) compared with the non-deletion genotype(21 patients) [33]. The authors also noted an excess broadband EEG power (1–32 Hz) peaking in the delta frequency range (peak frequency: 2.8 Hz), shared by both genotypes but stronger for the deletion genotype at younger ages to suggest non-UBE3A neuronal pathophysiology in deletion AS with more severe phenotype. However, EEG features such as delta activity, sleep spindles, etc. need to be evaluated more robustly for clinical relevance and reversibility before they can be used reliably in clinical trials as an objectively quantifiable measure.

4.2. Pseudo-hypsarrythmia

Misclassification of infantile spasms is possible due to the presence of a unique pseudo-hypsarrythmia pattern in EEG, which is seen particularly in 3 months-2 years old AS patients and can be differentiated from hypsarrythmia pattern by the following: predominance of slow waves compared to epileptiform discharges, no change in pattern between wakefulness and sleep, and lack of fragmentation during sleep [34].

EEG abnormalities associated with AS can also be seen rarely in some other epileptic encephalopathies such as Rett syndrome and 4p deletion syndrome [35,36].

5. Magnetic resonance imaging (MRI)

Neuroimaging abnormalities have been described in AS, such as corpus callosum hypoplasia, lateral ventricle enlargement, and cerebral atrophy(Fig. 2) [37]. Harting et al. reported five infants with delayed myelination and white matter deficit in a cohort of 9 AS patients (7.5 months − 5 years) [38]. Peters et al. reported diffuse white matter microstructure changes in AS by diffusion tensor imaging (DTI), and clinical severity was most correlated with the disruption in the temporal white matter pathway [39]. These microstructure changes were likely due to myelination defect as well as changes in the axonal density, diameter, and organization.

Fig 1. Representative EEG showing posterior dominant 3–4 Hz notched delta and theta activities (black arrow) and anterior dominant, rhythmic 2–3 Hz activities intermixed with spike-wave discharges (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
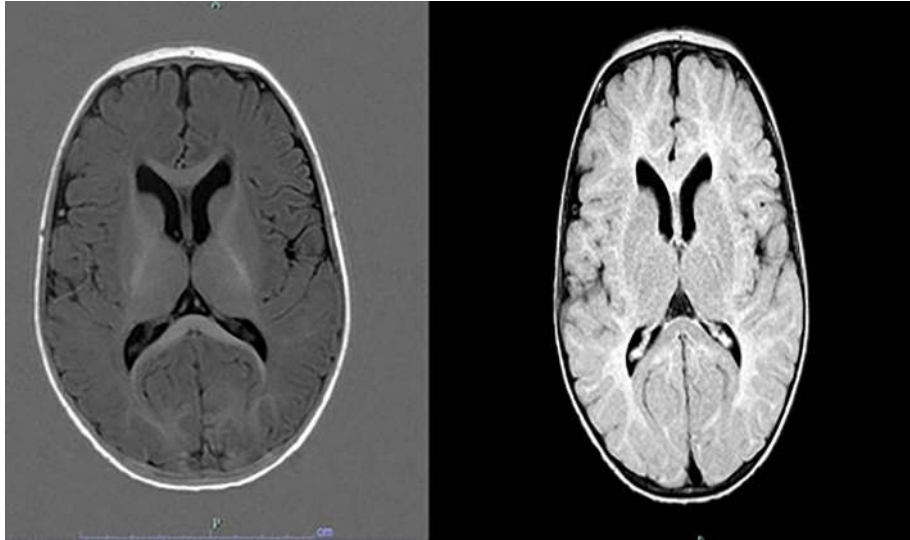
Fig. 2. MRI of a child with Angelman syndrome at the age of 8 months. Myelination on T1w(left) shows still deficient frontal and temporal white matter and a hypoplastic corpus callosum corresponding to a maturation stage of 5–6 months. T2w image(right) indicates mildly widened ventricles, dorsally thin corpus callosum, a slightly patchy T2 signal of the white matter with particular prominence over the parieto-occipital region.

6. Treatment

The effectiveness of individual AEDs in the treatment of seizures associated with AS is based on low-quality studies as prospective evaluations are scarce. Most retrospective chart-review and questionnaire-based studies have been beneficial to provide an understanding of relative efficacy and tolerability of one AED compared to others [40]. Considering underlying prominent GABAergic dysfunction, clinicians had used treatment that targets GABAergic signaling such as valproate, phenobarbital, and clonazepam as first-line therapies for AS [40]. However, due to unfavorable side effect profile of these former AEDs, other medicines such as topiramate, lamotrigine, ethosuximide, levetiracetam, clobazam (slightly different chemical structure than other benzodiazepines) have emerged as more favorable options.

6.1. Valproate

Previously valproate was used as one of the 1st line AEDs in the management of AS due to its effectiveness against various generalized seizures [2]. However, its use as first-line therapy is declining due to concern about adverse effects as well as the availability of other better tolerated AEDs for generalized epilepsy [41]. Valente et al. reported 18 patients (in a cohort of 19 patients) with improved seizure control from valproate either as a monotherapy or in combination with either clonazepam or phenobarbital. A clear trend of declining valproate use has been noted between 2 studies done in 2006–2007 and 2008–2015 [42,43]. Valproate use was

decreased from 60% to 40% in just one decade. In the 1st study, valproate was the most commonly used AED [43]. In the latter study, Shaaya et al. reported a cohort of 85 AS patients, among which 63 had epilepsy [42]. Twenty-five subjects (40%) were treated with VPA, and 2/3 of the patients had more than 90% seizure reduction, and the rest of them had more than 50% seizure reduction. However, unfortunately, greater than 70% had adverse events such as worsening behavior, ataxia, and declining gross/fine motor skills. Majority patients (60%) discontinued valproate due to adverse effects.

6.2. Topiramate

Thibert et al. reported that topiramate was the 2nd most commonly used AED (similar to clonazepam) following valproate in a questionnaire-based study [43] . Topiramate was used in 1/3 of patients. Topiramate has a GABA mimetic effect and can act as a positive allosteric modulator of GABA$_A$ receptors. Franz et al. reported a positive experience of treating 5 AS patients with topiramate [44]. All these patients had 15q11-13 deletions. 4 out of 5 patients were treated with topiramate monotherapy (6–23 mg /kg/day) over 3–12 months. One patient discontinued topiramate due to akathisia and insomnia. Besides the patient who discontinued topiramate, the rest of the patients had a remarkable improvement in seizures, and two patients remained seizure-free for 8–12 months. However, topiramate's cognitive side effects and appetite suppression remain a big concern in the AS patient population.

6.3. Lamotrigine

Lamotrigine use was noted in approximately ¼ AS patients in a questionnaire-based study [43]. Lamotrigine (a sodium channel blocker) has been effective for both focal and generalized epilepsy with broad activity against multiple seizure types associated with severe epileptic encephalopathies such as Lennox -Gastaut syndrome. Dion et al. retrospectively evaluated the effectiveness of adjunctive lamotrigine in 5 AS patients with intractable seizures [45]. Three patients became seizure-free, and one patient was seizure-free for one year with subsequent recurrence, and 1 had more than 50% reduction of seizure frequency in a low-dose but had worsening of seizures with a higher dose. Lamotrigine was relatively well-tolerated, and no patient had consistent worsening of seizures in spite of lamotrigine's potential pro myoclonic adverse effect. Although other sodium channel blockers such as phenytoin and carbamazepine are relatively contraindicated in AS patients due to potential worsening of absence and/or myoclonic seizure, it is unclear how lamotrigine shows positive response in AS consistently. Mechanisms other than sodium channel blockage have been speculated. In an MRS study, Kuzinecky et al. showed increased cerebral GABA concentration after four weeks of lamotrigine exposure in healthy volunteers [46]. Wang et al. showed that lamotrigine might increase the expression of *GABAB3* subunit expression in the hippocampus [47].

6.4. Ethosuximide

Ethosuximide, a T-type Ca^{2+} channel blocker, is the most preferred AED for typical absence seizures associated with childhood absence epilepsy. However, it has also been widely used for atypical absence seizures. Sugiura et al. demonstrated the use of high dose adjunctive ethosuximide (serum concentration greater than 110 mcg per mL) in combination with valproate for atypical absence seizures in 2 patients with AS [48]. Remarkable clinical improvement was noted in these patients in association with suppression of spike-wave complexes. Valproate may increase the level of ethosuximide, and the combination of valproate and ethosuximide may be preferable in patients with refractory absence seizures. Interestingly, ethosuximide has shown effectiveness in seizure control in mice with deficient *GABRB3* [9].

6.5. Levetiracetam

Levetiracetam is the most commonly used AED for any indication due to its broad activity against both focal and generalized seizures and favorable side effect profile with no or minimal occurrence of significant life-threatening adverse effects. Previously, levetiracetam has been used in approximately 20% of AS patients, but recently, this has emerged as the most commonly used AED in AS patients (used in 2/3 of the patients) [42,43]. In a retrospective study, levetiracetam was associated with a 90% reduction of seizures in 86% of patients [42]. However, 1/5 had behavioral adverse effects. Finally, 80% remained on levetiracetam therapy but only 1/3 on monotherapy with a dose range of 6.15–210 mg/kg/day to primarily support its role as a well-tolerated adjunctive AED.

6.6. Clonazepam

Clonazepam, an old and inexpensive 1,4-benzodiazepine, had been used extensively as a chronic AED in AS patients. In one study, clonazepam was the 2nd most commonly used AED in AS patients [43]. However, clonazepam's side effects, such as sedation, decreased muscle tone, and increased drooling, are not favorable for AS patients. Specifically, due to concern about tolerance, its use as a daily AEDs is declining in the developed world.

6.7. Clobazam

Clobazam, a 1,5-benzodiazepine, has been reported to exhibit less adverse effects and better tolerance profile than the classic 1,4-benzodiazepines such as diazepam and clonazepam. Clobazam had been very rarely utilized due to its unavailability in the United States previously. However, a recent study in the AS population showed this as the 2nd most commonly used AED (used in 50% of patients) after levetiracetam [42]. With exposure to clobazam, 93% had greater than 90% reduction in seizure frequency. Long term effect was evident, with 75% remained on the therapy and 1/3 on monotherapy. In this evaluation, tachyphylaxis was not found to be a significant factor.

6.8. Cannabidiol (CBD)

Acute CBD treatment (100 mg/kg (intraperitoneally) was noted to suppress hyperthermia and acoustically induced seizures in the AS mouse model but did not change myoclonic or tonic-clonic seizure susceptibility after kindling immediately and after two weeks of therapy [49]. A mild sedative effect was seen in the mice, and no definite improvement was noted in motor skill or memory secondary to CBD treatment. Interestingly, CBD treatment reversed some electrophysiological features, such as theta and delta slowing in the AS mice.

A highly purified form of pharmaceutical CBD has been approved for drug-resistant seizures associated with Dravet syndrome and Lennox-Gastaut syndrome [50,51]. Open-label trials of a pharmaceutical-grade CBD and other artisanal CBD products have shown long-term efficacy and safety of CBD in various other

treatment-resistant epilepsy such as tuberous sclerosis, CDKL5 deficiency disorders, Aicardi syndrome, 15q duplication, and Doose syndrome. Anecdotal reports exist about CBD's effectiveness in AS patients, but a rigorous randomized clinical trial is needed in the AS population. Some other new antiepileptic drugs such as rufinamide and perampanel have been utilized in small case series for management of nonepileptic myoclonus, but limited evidence currently exists for their efficacy against epileptic seizures [52].

6.9. Dietary therapies

The ketogenic diet can be very useful for the management of refractory seizures associated with AS [53]. Almost 1/3 of AS patients endorsed the ketogenic diet as the most successful treatment. However, tolerance may be a significant issue. Due to the restrictive nature of the ketogenic diet, Grocott and colleagues from the center for dietary therapy of epilepsy at the Massachusetts General Hospital evaluated 23 AS patients with low glycemic index dietary therapy [54]. Among these patients, three became seizure-free, and an additional 10 had only seizures in the presence of intercurrent infection. All these patients were treated with additional AEDs. Among the other eight patients, all had decreased seizure frequency after initiation of the diet except in one patient where detailed information was not available. Despite low ketone (beta-hydroxybutyrate) level, these patients had better seizure control to suggest an alternative mechanism of action, such as stabilization of blood glucose. Many patients tolerated higher than the required carbohydrate intake without any deleterious effect. Side effects (acidosis requiring supplementation with potassium citrate, carnitine supplementation, constipation) were benign, and compliance and tolerance were excellent with minimal rate of loss to follow-up. The robust effect of the low glycemic index diet was also noted in a prospective pediatric cohort of 6 AS patients [55].

6.10. Vagus nerve stimulation (VNS)

VNS has been utilized in medically intractable seizures. Tomei et al. reported a small case series of 3 AS patients treated with VNS [56]. All three patients had marked reduction of seizure frequency with improved alertness. No major side effect was reported. One patient even became clinically seizure-free. However, none of these patients could decrease their AEDs. Vagal hypertonicity has been speculated in AS secondary to a central mechanism or due to intrathoracic pressure changes associated with frequent laughter. Preoperative use of anticholinergics has been recommended as a unique management consideration for AS patients [57]. Although the vagal hypertonicity may indicate an increased risk of bradyarrhythmia, this has not been noted in clinical experience. On the contrary, augmented vagal responsiveness with better efficacy of VNS has been hypothesized in a study. Based on a survey-based study, Thibert et al. described 16 patients with VNS use, out of which 3 reported VNS as the most effective therapy. The exact mechanism of action of VNS in AS (as with any other forms of epilepsy) is unknown, but decreased excitability may be associated with improvement in GABAergic signal and inhibition of brainstem mediated fast synchronous oscillation (nucleus tractus solitarious mediated brainstem reticular formation activity). Chronic VNS administration has noted to be associated with increased cerebrospinal fluid(CSF) GABA levels and may be particularly relevant for the management of AS.

6.11. Corpus callosotomy

Palliative surgical procedures such as corpus callosotomy have been utilized for the management of intractable drop seizures and disabling falls associated with various types of generalized seizures. Although corpus callosotomy can cause an improvement in generalized tonic-clonic and atonic seizures in several epileptic encephalopathies, effectiveness and the role of corpus callosotomy in the management of AS is currently unknown due to paucity of good quality research.

6.12. Corticosteroid

Forrest et al. described four children with AS who showed excellent response to prednisone therapy [58]. Improvement in both clinical (decrease seizure frequency of spasms, atypical absence, and atonic seizures) and EEG appearance were seen. Moreover, improvement in sleep, myoclonus, development, and social interaction was noted. Activation of the GABA receptor by steroid has been hypothesized as a potential mechanism.

6.13. Management of nonconvulsive status epilepticus

Management of nonconvulsive status epilepticus is particularly important in AS patients. Worden et al. reported that approximately 50% AS patients had nonconvulsive status epilepticus with features of myoclonic or absence seizures [59]. This study showed the success of oral diazepam in the treatment of nonconvulsive status in ambulatory patients. In 13 pediatric patients with AS, a course of oral tapering diazepam (mean dose of 0.32 mg/kg /day in 2–3 divided doses over 4–12 days) successfully terminated 80% (20/25) episodes. No major side effects, such as respiratory depression was observed. Occasional patients required the 2nd course of therapy. If ambulatory treatment with diazepam fails, prednisone therapy has been tried and/or inpatient hospitalization

with more aggressive management, including therapeutic coma. Other than diazepam, alternative benzodiazepines such as clonazepam, clobazam, lorazepam, a higher dose of valproate, levetiracetam, and diet with carbohydrate restriction have been utilized for ambulatory and inpatient management of status.

6.14. AED induced worsening of seizures

Carbamazepine and oxcarbazepine can cause a worsening of seizures in AS patients. Interestingly vigabatrin, a GABAergic drug, does not effectively manage seizures in AS patients and may induce worsening of seizures [60]. Possibly increasing the GABA level without enhancing the GABA receptor function may be responsible for its ineffectiveness.

7. Outcomes

Several studies in AS reported severe seizures in early childhood with a distinct improvement during later childhood [61–63]. Seizure remission in late teens and early twenties followed by recurrence of seizures in third or fourth decades has been reported [64]. However, studies also described the persistence of subtle absence and myoclonic seizures throughout adulthood [65]. Larson et al. reported increase seizure frequency and severity in individuals over 25 years age compared to those 16–20 years old.

8. Future therapy

There is no approved curative treatment of AS, and available therapies for epilepsy are focused on the symptomatic management of seizures to minimize seizure frequency and severity. However, this field is rapidly changing, with advancements in various molecular therapies [66,67]. Discovery of the abnormal phosphorylation state of calcium/ calmodulin-dependent protein kinase II in AS demonstrated postnatal biochemical and signal abnormalities as a causative pathway for many phenotypes (rather than irreversible global developmental defects) and raised interest in AS therapeutics to rescue clinical phenotypes with postnatal intervention [68,69]. The characteristic of ideal therapy will be a minimally invasive intervention without significant toxicity that can cross the blood-brain barrier to produce a long-term, gene-specific regulation with a maximum and durable phenotypic reversal [70]. The treatment development can be categorized as follows: 1. Gene/protein replacement therapy (Adeno and lentiviral vector therapy to deliver a gene or secretory protein); 2. Activation of the intact but silent paternal copy of *UBE3A* (antisense oligonucleotide therapy and artificial transcription factors); and 3. Downstream therapies (OV101/gaboxadol, ketone supplement, novel compounds/peptides, anti-inflammatory/regenerative therapy) (Fig. 3).

8.1. AAV and other viral vector therapy (gene/protein replacement therapy)

The most common genetic abnormality of AS is de novo 5–7 Mb maternal loss of 15q11-13. However, it would be challenging to replace this large deleted region with viral vectors due to size limitation, and a pragmatic approach involves only the replacement of the causative *UBE3A* gene. Adenovirus associated virus serotype 9 (AAV-9), with the highest transgene expression in the brain compared to other serotypes, has been used with a TR-2 flank *UBE3A* to directly injected into the hippocampus of AS mice with an improvement of associative learning. AAV-9 therapy produced a limited distribution of viral vector in the brain and only achieved partial rescue of memory and learning but no improvement in motor coordination (possibly due to the AAV9 not reaching the cerebellum) [71]. Lentiviral vectors have also been proposed to deliver non-integrating episomes in the neurons. Rather than cDNA delivery, alternative approaches to providing the protein to rescue phenotype have been considered.

Besides the restriction of viral distribution around the injection site, another potential limitation is the immune reaction against AAV. Although the AAV study was encouraging to show partial phenotype reversibility, other less traditional approaches had been explored in search of full phenotypic rescue.

8.2. Reactivation of the intact but silent paternal copy of UBE3A

Paternal *UBE3A* is epigenetically silenced by a long antisense RNA transcript overlapping the open reading frame of paternal *UBE3A*. By using a screening method in primary cortical neurons of mice, Huang et al. identified several topoisomerase 1 and 2 inhibitors that can unsilence the paternal Ube3a by downregulating antisense transcript overlapping the paternal copy [72]. Among these topoisomerase inhibitors, an FDA approved cancer chemotherapy agent topotecan can powerfully turn on the inactivated paternal allele of *UBE3A* with improved Ube3a expression in several regions of the nervous systems, such as the hippocampus, neocortex, striatum, cerebellum, and spinal cord in a mouse model. The effect was evident chronically with an enduring impact of increased expression of Ube3a in spinal neurons for up to 12 weeks after intrathecal administration. As a chemotherapeutic agent, neutropenia and systemic toxicity are concerning side effects of Topotecan. Additionally, research has not been expanded to assess its potential off-target effects,
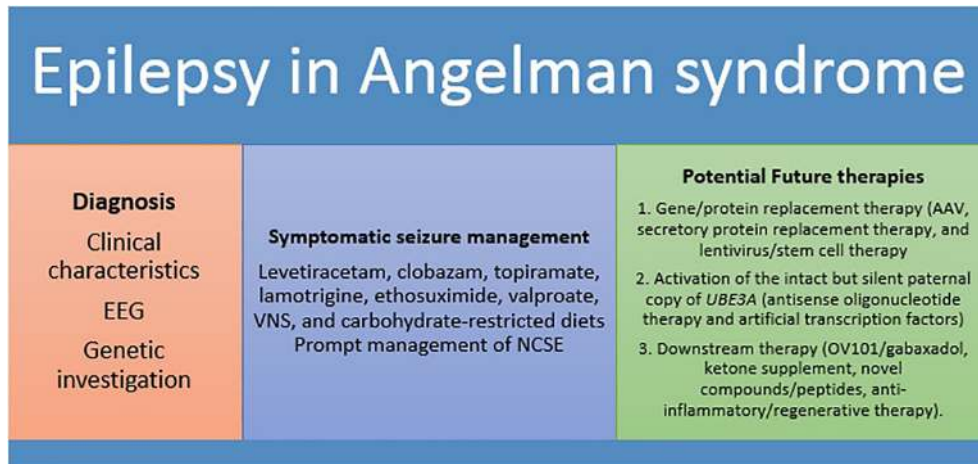
Fig 3. Current and potential future therapies in Angelman syndrome.

and no recent advancement toward human trials has been reported.

However, the concept of reducing *Ube3a-ATS* expression to improve paternal *Ube3a* expression has further augmented by other studies using a transcriptional termination signal [4,73]. Meng et al. reported the use of antisense oligonucleotide therapy by reduction of *UBE3A- ATS* (antisense transcript is an atypical transcript made by the nuclear-localized long non-coding RNA polymerase II) and sustained unsilencing of paternal antisense transcript in a murine model. The decrease in neuronal *UBE3A-ATS* was up to 90% within 48 h of treatment -both in vitro and in vivo examinations- as a dose-dependent manner after single intracerebral ventricular injection in adult mice. After four weeks of injection, partial restoration of *Ube3a* protein was observed. Following a single injection of antisense oligonucleotides(ASOs), decreased ATS expression persisted for four months in cortical neurons [74].

However, widespread and high-level cortical expression and Ube3a restoration remain a challenging task. Behavioral phenotypes were compared between ASO treated mice with controls. Although ASO treated mice showed some improvement in memory, they did not show significant improvement in many behavioral tests such as in the open field assay during testing for locomotor and anxiety-like behavior, in the marble-burying test during the examination of anxiety and obsessive-compulsive behaviors as well as during testing on an accelerating rotarod to evaluate motor coordination. A complete phenotypic reversal may need treatment before the closure of the critical window or may need a higher Ube3a induction level. Additionally, improvement may appear later than the testing period due to a gradual recovery of neuronal circuits, much delayed after the correction of the Ube3a protein.

8.3. Engineered DNA-binding protein (Artificial transcription factor/ATF)

AS is caused by mutation of a single gene and thus an ideal candidate for gene expression therapy, especially with advanced technology to engineer smaller DNA-binding particle such as artificial transcription factor (based on zinc finger, TALENS- Transcription activator-like effector nucleases, CRISPR/CAS9- clustered, regularly interspaced, short, palindromic repeats) that can cross the blood-brain barrier and inhibit *UBE3A-ATS* with subsequent expression of Ube3a [75]. Research studies involving mice using transcription factors are applicable to the future human research as the imprinting control centers are highly conserved among species. Bailus reported the use of an engineered Zinc finger-based artificial transcription factor in an adult mouse model [76]. After intraperitoneal or subcutaneous injection, these ATFs cross the blood-brain barrier with an improved expression of Ube3a in the hippocampus and cerebellum. CRISPR technology has been used to produce a large deletion *Ube3a* rats and AS pig models. Additionally, CRISPR /CAS13 b technology is gathering attention in the treatment sphere as it can cut RNA directly compared to CRISPR /CAS9 that can only cut DNA. However, several shortcomings exist, such as difficulty in the distribution of UBE3A throughout the neurons of the brain, potential off-target effect, and potential immune response against the agent. Additionally, more research is needed regarding the critical window of restoration [77]. Deng et al. reported the use of a mouse mesenchymal (bone marrow) stem-cell that can secrete an artificial transcription factor as a delivery platform to reactivate silent UBE3A with an enhanced expression of the protein in hippocampus, cerebellum, and cortex in a mouse model.

8.4. Downstream therapeutics

In conjunction with molecular therapy to increase UBE3A expression, several research groups have attempted to investigate therapeutics to attack synaptic abnormality associated with AS. This is particularly relevant as an alteration of synaptic physiology in AS may be similar to other neurodevelopmental disorders, and a broader application might be possible of the effective intervention.

Egawa et al. showed that selective extrasynaptic $GABA_A$ receptor agonist gaboxadol improved the abnormal firing properties of a population of Purkinje cells in cerebellar brain slices in *Ube3a*-deficient mice in vivo [12]. OV101/gaboxadol, a small molecule derived from muscimol (naturally found in mushroom), has been evaluated in the STARS study (a phase II RCT) over 12 weeks in adolescents and adults (13–49 years) AS patients and showed global improvement in a subjective improvement scale with a once-daily dose [78]. However, no specific data was available in terms of seizure control. Ganaxolone, another modulator of extrasynaptic $GABA_A$ receptors, also noted to decrease seizure susceptibility in AS mice in association with improvement in motor deficits [79].

A double-blind, placebo-controlled, trial investigated beneficial effects of two nutritional products (by potentially increasing methylation), betaine and folic acid, in 48 children with AS over one year but did not find any statistically significant changes between the two groups [80]. Patented synthetic analogs of cyclic glycine proline is a breakdown product of Insulin-like growth factor-1(IGF-1), which is a growth factor that's naturally present in the brain and can exert a widespread effect in biological process in the brain, such as reduction of neuroinflammation, action against overactivated microglia, and improvement of synaptic signaling. Although ketogenic and low glycemic index diets have been noted to be safe and effective in the management of AS patients, noncompliance and micronutrient deficiencies are challenging for chronic use. Although ketone ester supplementation reduced seizure activity in an AS mouse model, the effectiveness and safety of consumption of exogenous ketones in humans are unknown [81]. A 16 week double-blind, randomized control trial using beta hydroxybutyrate has been planned in AS patients. Similar to the fragile X mouse model, lovastatin suppressed the epileptiform activity and audiogenic seizures in an AS mouse model [82]. The supplementation of taurine has been studied in an AS mouse model [83,84].

Abnormal dendritic spine morphology and density in hippocampal pyramidal neurons leading to abnormal synaptic physiology have been described in AS. Minocycline, a second-generation tetracycline antibiotic medication, has been shown to recover aberrant synaptic function by reducing matrix metalloproteinases and positively altering dendritic spine structure [85]. In a prospective open-label study of minocycline, Grieco et al. showed improvement in communication and fine motor activities in 25 AS children (4–12 years), but the Phase II, randomized trial for minocycline therapy up to 16 weeks failed to show significant improvements in the developmental status of the patients or in the EEG [85,86]. Patients with uncontrolled seizures were excluded from the study.

9. Conclusion

Current therapy of intractable epilepsy associated with AS is primarily symptomatic. However, in the last 20 years, there has been remarkable progress in the understanding of causative gene, elucidation of subsequent signal abnormalities, and the delineation of paternal *UBE3A* gene silencing: essential discoveries not only for the management of epilepsy but likely improvement in the health of AS patient as a whole. Several biotechnology companies have received orphan drug designation of various products from the FDA and European Commission for faster development of commercially viable therapeutics. There has been significant progress in the establishment of a global patient registry to identify suitable patients for recruitments in the clinical trials [87,88]. However, proper cost-effective analysis is needed to balance the economic burden of the disease with these potential ultra-costly therapeutics.

Disclosures

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Declaration of Competing Interest

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests: The author is supported by the Translational Research Institute (TRI), grant UL1 TR003107 through the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH). The content is solely the respon-

sibility of the authors and does not necessarily represent the official views of the NIH.

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