ANGELMAN SYNDROME CLINICAL CARE TOOL KIT

The Angelman Syndrome Foundation (ASF) shares with you today with great enthusiasm and a deep sense of purpose to introduce a comprehensive Clinical Care Toolkit for the Angelman Syndrome (AS) community, which I believe will greatly benefit both patients and the medical professionals who care for them.

As a passionate advocate for individuals with Angelman Syndrome, I have witnessed firsthand the challenges faced by both the patients and their healthcare providers. Angelman Syndrome is a complex neurodevelopmental disorder that requires specialized knowledge and a multidisciplinary approach to care. Recognizing the need for a standardized resource that can improve clinical practice and enhance patient outcomes, I have collaborated with experts in the field to develop the Angelman Syndrome Clinical Care Toolkit.

This toolkit is designed to provide physicians and healthcare professionals with a comprehensive and up-to-date guide to the diagnosis, treatment, and management of Angelman Syndrome. It covers a wide range of topics, including:

- **Overall Standards of Care in AS**
- **Seizure Treatment Guideline**
- **Management of Nonconvulsive Status Epilepticus in AS**
- **General Anesthesia Best Practice**
- **Myoclonus in Angelman Syndrome**
- **PT and OT Best Practices**
- **LADDER Learning Network**

The Angelman Syndrome Clinical Care Toolkit has been developed in close collaboration with leading medical professionals through the LADDER Learning Network, researchers, and the ASF. It is based on the most current scientific evidence and clinical experience, providing a trusted resource that can support and empower healthcare providers in their care of individuals with Angelman Syndrome.

I invite you to explore its contents and consider integrating it into your practice. By utilizing this toolkit, you can enhance the quality of care you provide to your patients with Angelman Syndrome, improving their overall well-being and long-term outcomes.

We believe that by equipping healthcare professionals with this invaluable resource, we can create a positive impact on the lives of individuals with Angelman Syndrome and their families. I kindly request your support in sharing the Angelman Syndrome Clinical Care Toolkit with your colleagues and medical staff who may also benefit from this comprehensive guide.

Thank you for your time, consideration, and dedication to the well-being of individuals with Angelman Syndrome. Should you have any questions or require additional information, please do not hesitate to contact me.

Together, we can make a difference and ensure that individuals with Angelman Syndrome receive the highest standard of care they deserve.

Sincerely,
AMANDA MOORE, CEO

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OVERALL STANDARDS OF CARE IN ANGELMAN SYNDROME

angelman
SYNDROME FOUNDATION

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REVIEW ARTICLE

A multidisciplinary approach and consensus statement to establish standards of care for Angelman syndrome

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Abstract

Background: Angelman syndrome (AS) is a rare neurogenetic disorder present in approximately 1/12,000 individuals and characterized by developmental delay, cognitive impairment, motor dysfunction, seizures, gastrointestinal concerns, and abnormal electroencephalographic background. AS is caused by absent expression of the paternally imprinted gene *UBE3A* in the central nervous system. Disparities in the management of AS are a major problem in preparing for precision therapies and occur even in patients with access to experts and recognized clinics. AS patients receive care based on collective provider experience due to limited evidence-based literature. We present a consensus statement and comprehensive literature review that proposes a standard of care practices for the management of AS at a critical time when therapeutics to alter the natural history of the disease are on the horizon.

Methods: We compiled the key recognized clinical features of AS based on consensus from a team of specialists managing patients with AS. Working groups were established to address each focus area with committees comprised of providers who manage >5 individuals. Committees developed management guidelines for their area of expertise. These were compiled into a final document to provide a framework for standardizing management. Evidence from the medical literature was also comprehensively reviewed.

Results: Areas covered by working groups in the consensus document include genetics, developmental medicine, psychology, general health concerns, neurology (including movement disorders), sleep, psychiatry, orthopedics, ophthalmology, communication, early intervention and therapies, and caregiver health. Working groups created frameworks, including flowcharts and tables, to help with quick access for providers. Data from the literature were incorporated to ensure providers had review of experiential versus evidence-based care guidelines.

Conclusion: Standards of care in the management of AS are keys to ensure optimal care at a critical time when new disease-modifying therapies are emerging. This document is a framework for providers of all familiarity levels.

KEYWORDS
Angelman Syndrome, genetics, management, neurogenetics, UBE3A

1 | INTRODUCTION

Angelman syndrome (AS, MIM# 105830) is a neurogenetic disorder impacting approximately 1/12,000 to 1/20000 (Steffenburg et al., 1996). Diagnosis of classic AS is often made between 1 and 2 years of age, often later with non-classical presentation (Gentile et al., 2010). Characteristic features include developmental delays especially in expressive language, a distinctive happy demeanor, seizures, gross and fine motor deficits, tremors, sleep disturbances, gastrointestinal problems, stereotypical behavior, anxiety, and hyperkinesis.

The ubiquitin protein E3A ligase gene (*UBE3A*) is paternally imprinted in neurons, and the clinical features of AS are primarily due to deficient maternally expressed UBE3A protein in the brain. *UBE3A* is located on chromosome 15q11.2q13 and encodes three EA6P protein isoforms via differential splicing (Copping et al., 2017; Dindot et al., 2008; Hillman et al., 2017; Yamamoto et al., 1997). There are four recognized molecular mechanisms: (a) deletion of maternal 15q11.2q13 (70–75%); (b) mutation of maternal *UBE3A* gene (15%) with a 50% recurrence risk if maternally inherited; rarely (c) paternal uniparental disomy (UPD, 5–7%); and (d) imprinting defect (ImpD, 5–7%) due to an epimutation conferring an aberrant paternal imprint onto the maternal *UBE3A*, or less commonly due to deletion of the imprinting center with a 50% risk of recurrence if maternally inherited. Mosaicism is primarily associated with an epimutation (Aypar et al., 2016; Camprubi et al., 2007; Carson et al., 2019; Fairbrother et al., 2015). Features vary depending upon molecular subtype (Bindels-de Heus et al., 2020; Larson et al., 2015; Sahoo et al., 2007; Tan et al., 2011). Figure 1 presents a diagnostic algorithm. Genetic counseling should be offered to all families to discuss recurrence risk, which differs based on molecular subtype.

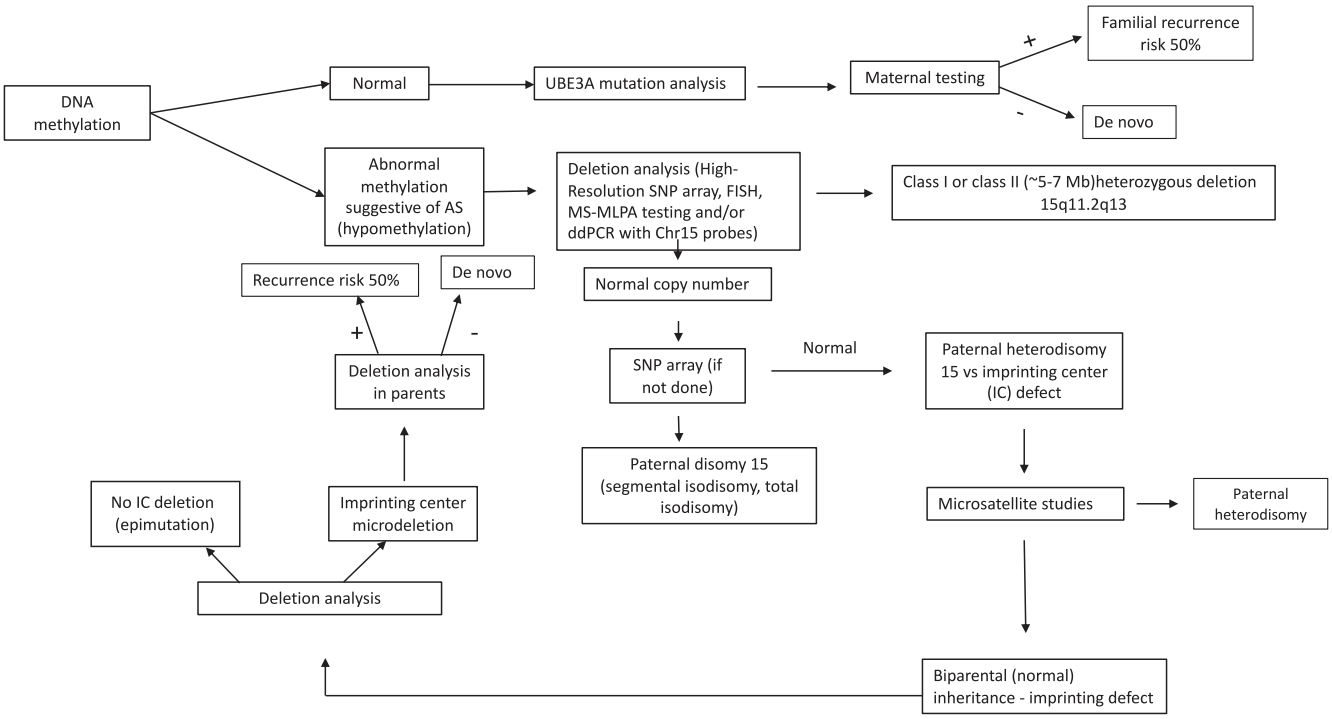

FIGURE 1 Angelman Syndrome (AS) Genetic Testing Algorithm. Guidance to work up when considering a diagnosis of AS. Abbreviations: FISH Fluorescence in situ hybridization; SNP single nucleotide polymorphism; MS methylation-specific; MLPA multiplex ligation-dependent probe amplification; PWS Prader-Willi Syndrome; AS Angelman syndrome; UPD uniparental disomy; *UBE3A* ubiquitin protein ligase E3A gene.

This recommendation aims to highlight standardization of care in preparation for personalized therapies. The Food and Drug Administration recommends establishing an accessible document with an expert statement regarding treatment.

2 | METHODS

The consensus of care across the lifespan reflects the compilation of input from more than 20 key opinion leaders (KOLs) in the field. The document was circulated to experts across the globe for feedback and revision. All co-authors met at least one of the following criteria: (a) substantial clinical experience working with children and adults with AS (operationalized as having seen at least 5 individuals in both consultation and follow-up) and (b) willingness to practice evidence-based medicine with comprehensive review of the literature.

Literature review was performed in PubMed and Ovid Medline. PubMed search terms included (Angelman Syndrome) AND (Management OR treatment OR clinical trial OR medication OR behavioral OR intervention), yielding 1,273 articles. The Ovid search terms included Angelman Syndrome/dg, dh, dt, pc, th [Diagnostic Imaging, Diet Therapy, Drug Therapy, Prevention & Control, Therapy] AND (Management OR treatment OR clinical trial OR medication OR behavioral OR intervention).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] and yielded 59 results. Articles included were clinical trials, retrospective case reviews, meeting abstracts, and case series focused on the management of AS. The final review included removal of duplicates and sorting for relevance to human management and yielded 100 articles.

3 | REVIEW AND PRACTICE GUIDELINES

Through data gathered in natural history studies and clinical experience, the clinical description continues to evolve to include newly recognized features. Due to the limited nature of relevant references and a lack of evidence base, KOL experience was prioritized over the literature review, but both were considered. A limited number of clinical trials to support practices were available, and therefore, the evidence level is III (controlled trials without randomization) or IV (designed case-control or cohort studies).

3.1 | General considerations

Table 1 shows comprehensive management by age.

3.1.1 | Feeding

AS may present with hypotonia and failure to thrive (FTT) in infancy, but conservative treatment is usually sufficient. Sucking, chewing, and swallowing can be abnormal, including failure to breastfeed due to inadequate latching. Tongue protrusion and dyspraxia of swallowing and breathing during feeding contribute to FTT, and silent aspiration may occur. Early involvement of a feeding therapist is recommended. A feeding tube should be approached cautiously but considered when there is a history of aspiration pneumonia (Bindels-de Heus et al., 2020; Glassman et al., 2017). Feeding tubes are required more commonly in individuals with a deletion. Choking remains a risk throughout life due to the combination of not chewing properly and stuffing the mouth.

3.1.2 | Growth

Height is usually normal (Bindels-de Heus et al., 2020; Mertz et al., 2013; Tan et al., 2011). Disproportionately slow head growth may lead to microcephaly (≤−2 SDS) by age 2 years, particularly in those with deletion subtype. Absence of microcephaly is insufficient for rejection of a clinical suspicion of AS, especially in the non-deletion subtypes (Williams et al., 2006).

3.1.3 | Hormones and puberty

The timing of puberty and menarche is normal. Regularity, duration, and severity of menses in females are typical (Kaskowitz et al., 2016). Hormonal alterations of puberty can affect epilepsy, anxiety, and behavior. Regulation of menses may be beneficial due to hygiene and impaired comprehension. Oral contraceptives and intramuscular progestogens are options, the latter with consideration of possible negative effect on bone health. Subdermal and intrauterine hormonal devices require anesthesia for initiation but are long-acting, effective options. Discussing options with a gynecologist and/or endocrinologist is advised. Requests for permanent sterilization require formal consultation with experts in reproductive ethics as this is often not recommended (Albanese & Hopper, 2007; Kaskowitz et al., 2016). In adult males, public masturbation can be problematic and behavioral modifications are typically

TABLE 1 Health considerations by age for individuals with Angelman syndrome

Age	Medical eval	Anticipatory guidance	Medical referrals	Labs	Diagnostic	Medication/ supplement considerations
Age of diagnosis	• Feeding • Vision - CVI - strabismus • GERD • Growth & Development • Tone • Seizures	• Genetic counseling • Hold upright during feeding and for 30 minutes after feeding (GERD precautions) • Discuss low-carbohydrate, higher protein and fat foods towards implementation of LGIT diet • Early intervention services • Assess sleep • Seizures precautions/management • Monitor constipation • Sufficient environmental stimulation • Support groups • Clinical research[a]	• Genetics/Genetic Counseling • Neurology • Ophthalmology • GI/Nutrition • OT - Address sensory needs • PT - Orthotics - Aqua therapy • SLP - AAC	• Genetic confirmation (See Figure 1) • If failure to thrive is present: CMP, CBC, thyroid studies, vitamin D, magnesium, phosphorus • Assess patient produces ketones as expected if initiating diet: acylcarnitine profile, urine organic acids, free and total carnitine • Additional labs before initiating/monitoring diet: selenium, zinc, ionized calcium, BHB, lipid panel, carnitine, urine calcium • Ferritin with ESR	• Hip x-ray (especially if not ambulatory) • Spine x-ray • EEG, especially if suspect seizures • Feeding evaluation - VFSS if needed	• Diet: LGIT or ketogenic diet • Seizure management (see Figure 2) • MCT oil to support diet/ constipation • Levocarnitine if level borderline or low in patient on low carbohydrate diet
1–3 years old	• Growth & development • Vision - CVI - strabismus • Feeding • Seizures • Sleep • Behavior	• Early intervention services • LGIT/ketogenic diets • Routines - Bedtime - Toileting (see Figure S1) - Daily activities - Behavioral modification • Limit-setting • Seizures • Support groups • Clinical research[a]	• Neurology • Medical Home/AS specialist • Ophthalmology • Developmental Pediatrician • GI/Nutrition • Sleep (if not addressed by another specialist) • OT - Address sensory needs • PT - Orthotics - Aqua therapy - hippotherapy • SLP - AAC • Vision therapy • Equipment referral (specialized stroller, car seat, Safe sleep bed) • Applied behavioral analysis/ behavioral therapy • Dental care	• Ferritin and ESR • CBC • Vitamin D • Diet Monitoring - CBC - Vitamin D - CMP - Selenium - Magnesium - Phosphorus - Zinc - Carnitine - BHB - Lipid panel - Urine calcium - Ionized calcium	• Hip x-ray (especially if not ambulatory) • Spine x-ray • Consider EEG • Feeding evaluation	• Diet: LGIT or ketogenic diet • Seizure management (see Figure 2) • MCT oil to support diet/ constipation • Levocarnitine if level borderline or low in patient on low carbohydrate diet • Sleep Management (see Figure 3) • Consider transition to Safe Sleep bed • Behavior Management (see Figure 4) • Treat constipation with stool softener +mild stimulant (e.g. senna, magnesium)

Age	Medical eval	Anticipatory guidance	Medical referrals	Labs	Diagnostic	Medication/ supplement considerations
5–13 years-old	• Growth & development • Seizures • Sleep • Behavior • Vision • Scoliosis • Mobility • Weight management	• Seizures • Non-epileptic myoclonus may emerge around the time of puberty • Sleep • LGIT/ketogenic diets • Hyperphagia • Constipation • Mobility (change in gait pattern, consider pain) • Constipation (can be linked to sleep disturbance, seizures, behavior changes) • Anxiety • Puberty - Monitor seizures - Behavior changes - Plan for suppression of menses (in females) • Routines/consistency in all environments - Bedtime - Toileting (see Figure S1) - Daily activities - Behavioral modification strategy - Safety plan (tracking if elopement is a concern) • IEP intervention - PT[b] - SLP: AAC integration - OT: focus on independence, activities of daily living - Para pro - Inclusion where appropriate - Functional behavioral assessment and ABA/behavioral therapy services - Seizure plan (prophylactic medications) • Clinical Research[a]	• Neurology • Medical Home/AS specialist • Ophthalmology • GI/Nutrition • Sleep (if not addressed by another specialist) • Orthopedics (as needed for mobility, scoliosis, DDH) • Obstetrics & gynecology • SLP - AAC focus • OT • PT - Orthotics - strengthening - Aqua therapy - Hippotherapy - SPIDER therapy • Vision therapy • Applied behavioral analysis/ behavioral therapy • Dental care • IEP advocate	• Ferritin and ESR • Vitamin D • CMP • CBC • Lipid panel • Diet Monitoring - CBC - Vitamin D - CMP - Selenium - Magnesium - Phosphorus - Zinc - Carnitine - BHB - Lipid panel - Urine calcium - Ionized calcium	• Hip x-ray (especially if not ambulatory) • Spine x-ray • NEM: rule out underlying causes – constipation, worsening sleep, decreased appetite and poor nutrition, changes in mobility related to decreased ROM and pain) • DEXA every 2 years if on low carbohydrate diet long-term, non-ambulatory, delayed puberty or history of >2 fractures	• Diet: LGIT or ketogenic diet • Seizure management (see Figure 2) • MCT oil to support diet/ constipation • Levocarnitine if level borderline or low in patient on low carbohydrate diet • Sleep Management (see Figure 3) • Consider transition to Safe Sleep bed • Behavior Management (see Figure 4) • Treat constipation daily with stool softener +mild stimulant (e.g. senna)

(Continues)

TABLE 1 (Continued)

Age	Medical eval	Anticipatory guidance	Medical referrals	Labs	Diagnostic	Medication/ supplement considerations
1–5 years old	• Growth & development • Seizures • Vision - CVI - strabismus • Feeding • Scoliosis • Sleep • Behavior • Mobility	• Early intervention services/IEP preparation • Seizures • LGIT/ketogenic diets • Routines - Bedtime - Toileting (see Figure S1) - Daily activities - Behavioral modification strategy • Limit-setting • Constipation (can be linked to sleep disturbance, seizures, behavior changes) • Activity - Adaptive sports - Exercise 30–90 minutes per day • Monitor gait over time • Sleep - Consider role of seizures at night • Support groups • Clinical research[a]	• Neurology • Medical Home/AS specialist • Developmental Pediatrician (if not addressed by another specialist) • Sleep (if not addressed by another specialist) • Ophthalmology • GI/Nutrition • SLP - AAC focus • OT • PT - Orthotics - strengthening - Aqua therapy - Hippotherapy - SPIDER therapy • Vision therapy • Applied behavioral analysis/ behavioral therapy • Dental care	• Ferritin and ESR • Vitamin D • Diet Monitoring - CBC - Vitamin D - CMP - Selenium - Magnesium - Phosphorus - Zinc - Carnitine - BHB - Lipid panel - Urine calcium - Ionized calcium	• Hip x-ray (especially if not ambulatory) • Spine x-ray • Consider EEG • Feeding evaluation • Consider sleep study (best if in home environment) • DEXA scan every 2 years if on low carbohydrate diet	• Diet: LGIT or ketogenic diet • Seizure management (see Figure 2) • MCT oil to support diet/ constipation • Levocarnitine if level borderline or low in patient on low carbohydrate diet • Sleep Management (see Figure 3) • Consider transition to Safe Sleep bed • Behavior Management (see Figure 4) • Treat constipation daily with stool softener +mild stimulant (e.g. senna)

Age	Medical eval	Anticipatory guidance	Medical referrals	Labs	Diagnostic	Medication/ supplement considerations
13–21 years-old	• Independence with ADLs • Transition • Seizures • Sleep • Behavior • Scoliosis • Mobility • AAC use and integration • Weight management	• Seizures • Non-epileptic myoclonus may emerge around the time of puberty • Sleep • LGIT/ketogenic diets • Hyperphagia • Constipation • Mobility (change in gait pattern, consider pain) • Constipation (can be linked to sleep disturbance, seizures, behavior changes) • Anxiety • Puberty - Monitor seizures - Behavior changes - Plan for suppression of menses (in females) • Routines/consistency in all environments • Bedtime • Toileting (see Figure S1) • Daily activities • Behavioral modification strategy • Safety plan (tracking if elopement is a concern) • IEP intervention • PT[b] • SLP: AAC integration • OT: focus on independence, ADL • Para pro • Inclusion where appropriate • Functional behavioral assessment and behavioral therapy services • Seizure plan (prophylactic medications) • Clinical Trials • Socialization • Vocational opportunities • Guardianship • Transition of care • Support groups • DDA services • Clinical Research[a]	• Neurology • Medical Home/AS specialist • Ophthalmology • Sleep (if not addressed by other specialist) • GI/Nutrition • Orthopedics (as needed for mobility, scoliosis) • Obstetrics & gynecology • SLP - AAC focus • OT - Focus on function and ADLs • PT - Orthotics - strengthening - Aqua therapy - Hippotherapy - SPIDER therapy • Applied behavioral analysis/ behavioral therapy • Dental care • IEP advocate	• Ferritin and ESR • Vitamin D • Diet Monitoring - CBC - Vitamin D - CMP - Selenium - Magnesium - Phosphorus - Zinc - Carnitine - BHB - Lipid panel - Urine calcium • Ionized calcium	• Spine x-ray • NEM: rule out underlying causes – constipation, worsening sleep, decreased appetite and poor nutrition, changes in mobility related to decreased ROM and pain) • DEXA every 2 years if on low carbohydrate diet long-term, non-ambulatory, delayed puberty or history of >2 fractures	• Diet: LGIT or ketogenic diet • Seizure management (see Figure 2) • MCT oil to support diet/ constipation • Levocarnitine if level borderline or low in patient on low carbohydrate diet • Sleep Management (see Figure 3) • Consider transition to Safe Sleep bed • Behavior Management (see Figure 4) • Treat constipation daily with stool softener +mild stimulant (e.g. senna)

(Continues)

TABLE 1 (Continued)

Age	Medical eval	Anticipatory guidance	Medical referrals	Labs	Diagnostic	Medication/ supplement considerations
Adults	• Independence with ADLs • Seizures • Sleep • Behavior • Scoliosis • Mobility • AAC use and integration • Weight management	• Non-epileptic myoclonus • Sleep • LGIT/ketogenic diets • Hyperphagia • Constipation • Mobility (change in gait pattern, consider pain) • Introduction and/or use of AAC • Constipation (can be linked to sleep disturbance, seizures, behavior changes) • Anxiety • Puberty - Monitor seizures - Behavior changes - Plan for suppression of menses (in females) • Routines/consistency in all environments - Bedtime - Toileting (see Figure S1) - Daily activities - Behavioral modification strategy - Safety plan (tracking if elopement is a concern) • Seizures • Socialization • Vocational training • Guardianship • Transition of care • Support groups • DDA • Preventive Medicine for adults - Breast examination/ mammograms - Prostate examination - Colonoscopy • Clinical research[a]	• Medical Home/AS specialist • Neurology • Ophthalmology • Sleep (if not addressed by other specialist) • GI/Nutrition • Orthopedics (as needed for mobility, scoliosis) • Obstetrics & gynecology • SLP - AAC focus • OT - Focus on function and ADLs • PT - Orthotics - strengthening - Aqua therapy - Hippotherapy - SPIDER therapy • Applied behavioral analysis/ behavioral therapy • Dental care	• Ferritin and ESR • Vitamin D • Diet Monitoring - CBC - Vitamin D - CMP - Selenium - Magnesium - Phosphorus - Zinc - Carnitine - BHB - Lipid panel - Urine calcium - Ionized calcium	• Spine x-ray • Consider EEG • Consider sleep study (best if in home environment) • NEM: rule out underlying causes – constipation, worsening sleep, decreased appetite and poor nutrition, changes in mobility related to decreased ROM and pain) • DEXA every 2 years if on low carbohydrate diet long-term, non-ambulatory, delayed puberty or history of >2 fractures • DEXA scan for females >65 years old to screen for osteoporosis	• Diet: LGIT or ketogenic diet • Seizure management (see Figure 2) • MCT oil to support diet/ constipation • Levocarnitine if level borderline or low in patient on low carbohydrate diet • Sleep Management (see Figure 3) • Consider transition to Safe Sleep bed • Behavior Management (see Figure 4) • Treat constipation daily with stool softener +mild stimulant (e.g. senna) • Preventive healthcare as guidelines recommend for adults (e.g. Pap smear, prostate screening, breast exam, mammogram, colonoscopy); however, anesthesia is required

Abbreviations: AAC, augmentative and assistive communication device; ABA, applied behavioral analysis; ADL, activity of daily living; AS, Angelman Syndrome; BHB, beta-hydroxybutyrate; CBC, complete blood counts; CMP, comprehensive metabolic panel; CVI, cortical visual impairment; DDA, Developmental Disabilities Administration; DEXA, dual-energy x-ray absorptiometry; ESR, erythrocyte sedimentation rate; GERD, gastroesophageal reflux disease; GI, gastroenterology; IEP, individualized education plan; LGIT, low glycemic index therapy; MCT, medium chain triglycerides; NEM, non-epileptic myoclonus; OT, occupational therapy; PT, physical therapy; SLP, speech & language pathology; SPIDER, Strengthening Program of Intensive Developmental Exercises and Activities for Reaching Maximal Potential; VFSS, video fluoroscopic swallow study.

[a]Clinical research opportunities include participation in the Global Angelman Registry, Natural History Study, and currently recruiting clinical trials.

[b]PT involvement providing support as needed in collaboration with IEP team to maximize participation within classroom and access of school environment.

attempted initially (Smith, 2001). Use of medications such as selective serotonin reuptake inhibitors with decreased libido as a side effect may be helpful. Antiandrogen therapy is not recommended. Fertility in individuals with AS is presumably normal. Their sociable disposition and cognitive impairment make them vulnerable to abuse (Smith, 2001). Regular Pap smear and gynecological exam under anesthesia is recommended per general guidelines, as individuals have a similar lifetime risk of uterine cancer to the general population.

3.1.4 | Immunization

Patients with AS have no evidence of immunodeficiency. Regular vaccination schedules are recommended, including vaccination for seasonal pathogens. COVID-19 vaccination is recommended.

3.1.5 | Heat intolerance

Individuals with AS tend to overheat, presenting as flushing and diaphoresis. Predisposition to dehydration lowers seizure threshold. Breathable clothing is advised, including during sleep when overheating impacts sleep quality. Strategies to manage heat intolerance include limiting time outdoors when hot, encouraging intake of cold fluids, fans, water mist, cool rags, visors, sunglasses, and UV protective clothing.

3.1.6 | Toileting

In the literature, daytime urinary continence is reported in 35% but clinical experience suggests 75% (Radstaake et al., 2013). Regular toilet visits, diaper removal, positive reinforcement, and close monitoring contribute to success in continence (Radstaake et al., 2014). All toileting activities should be encouraged in the restroom including diaper changes. Strategies also include Applied Behavioral Analysis (ABA) to work on routine and reward-based interventions (Radstaake et al., 2014; Warzak et al., 2016). Nighttime urinary continence is less common but facilitated by fluid restriction after dinner and toileting before bedtime. Please refer to Supplemental Figure I for guidance to an approach to toilet training (Figure S1).

3.1.7 | Dental

Brushing after teeth erupt is challenging. A double sided or electric toothbrush may be better tolerated. Mouthing, chewing, and gastroesophageal reflux disease (GERD) can cause erosion of the enamel. Drooling, causing continuous rinsing of the teeth, is a positive factor in dental hygiene. AS individuals may require sedation or anesthesia to conduct dental examinations and procedures, but this should not delay care (Khan et al., 2019).

3.1.8 | Anesthesia

Complications of anesthesia are rare, and typical management by the anesthesiologist is generally safe (Errando et al., 2007; Gardner et al., 2008; Kemper et al., 2010; Kim et al., 2010; Makris et al., 2018; Patil & Sindhakar, 2008; Rosado Fuentes et al., 2009; Warner et al., 2017; Witte et al., 2011). Specific intraoperative considerations associated with anesthesia include GABA receptor involvement in AS, since many intravenous and inhaled anesthetic agents modulate these receptors. Malignant bradyarrhythmias have been reported. Additional concerns include bradycardia due to increased vagal tone and delayed response to atropine (Gardner et al., 2008). A recent retrospective review suggests atypical responses to benzodiazepines, with one patient requiring flumazenil rescue; complications regarding airway management with one patient requiring videolaryngoscopic intubation; and a 2-year-old with intraoperative bronchospasm(Warner et al., 2017). Insufficient evidence exists to make specific anesthetic recommendations.

3.2 | Epilepsy and movement disorders

Epilepsy occurs in up to 90% of individuals and is most common in those with a deletion (Bindels-de Heus et al., 2020; Khan et al., 2019; Pelc et al., 2008; Williams, 2005; Williams et al., 2006). The mean age at onset of seizures was 1.7 years of age (range 3 months to 5 years) (Khan et al., 2019). Although at least 80–90% of children with deletions will develop epilepsy, the prevalence of seizures with mutations and UPD is up to 75%, and up to 50% for those with ICD (Thibert et al., 2009). Although the rate of seizures in the non-deletion group is lower than the deletion group, 15% of seizures in the non-deletion subtype had onset after age 5 years (equals 5% of all seizures, unpublished Rare Diseases Clinical Research Network).

For up to 1/3 of individuals, the first seizure will occur in the setting of a febrile illness (Thibert et al., 2013). Seizures tend to improve after puberty with a case series of 53 adults showing 65% resolution beginning at an average age of 16 years (Prasad et al., 2018). Seizure types at initial seizure presentation include myoclonic—25%,

atonic—23%, generalized tonic-clonic—21%, and atypical absences—12%. There are case reports of infantile spasms, but this seizure type is generally rare in AS. AS seizures are typically generalized, but up to 30% may also have focal seizures (Conant et al., 2009; Khan et al., 2019; Matsumoto et al., 1992; Pelc et al., 2008; Pollack et al., 2018; Prasad et al., 2018; Ranasinghe et al., 2015;9:142.; Sugimoto et al., 1992; Thibert et al., 2009, 2013).

Non-convulsive status epilepticus (NCSE) is common, typically consisting of periods of decreased responsiveness or alertness, which may last hours to days, often with loss of developmental skills (Fujikawa et al., 2003; Ohtsuka et al., 2005; Yang et al., 2010). NCSE typically presents with few to no clinical seizures, so it may go unrecognized. While rates of NCSE have been reported in 50–90% of the population in older studies, a very recent study of 100 AS children followed over 7 years found that 19% had an episode of NCSE, while 5% experienced convulsive status epilepticus (Bindels-de Heus et al., 2020). In a case series of 104 children in 2018, the rate was 20% (Worden et al., 2018). Rarely, NCSE will be accompanied by frequent myoclonic jerks, which is known as myoclonic status in non-progressive encephalopathies (MSNPE)(Caraballo et al., 2007).

In addition to myoclonic seizures and MSNPE, individuals also have non-epileptic myoclonus (NEM) most consistent with a movement disorder. Myoclonic seizures occur in younger age groups, whereas NEM occurs during adolescence and adulthood (Pollack et al., 2018). Both can be disabling, but myoclonic seizures have an EEG correlate and are generally controlled with medication as compared to NEM, which has no EEG correlate and can be disabling and refractory, though there is no alteration in consciousness (Casara et al., 1995; Pollack et al., 2018). Although evidence is lacking, experience suggests patients may benefit from medications effective in treating myoclonic seizures, such as levetiracetam, clobazam, and clonazepam, but the mainstay of therapy is to minimize triggers, such as poor sleep, GI dysfunction, and anxiety. A recent publication suggests a possible benefit of perampanel in the treatment of NEM (Kawano et al., 2020). In addition to NEM, AS movement disorders include tremor, ataxia, and possibly dystonia.

Evaluation for seizures includes an EEG, which is characterized by high amplitude slow (delta and theta) waves and a relative lack of normal background rhythms. High voltage (>300 microvolts) slowing with a "notched" delta (1–3 Hz) pattern is present in over 90% of individuals and provides a diagnostic clue (Korff et al., 2005; Laan et al., 1997; Sidorov et al., 2017; Thibert et al., 2013; Valente et al., 2003; Vendrame et al., 2012; Wang et al., 2005). Long-term video EEG recording helps determine if a behavioral episode is a seizure or a non-epileptic event. Blood chemistry and complete blood count testing exclude metabolic triggers and offer a baseline. Lumbar puncture and brain imaging are not indicated unless considering other etiologies.

There are no comparative trials of the various anticonvulsant drugs (ACDs); thus, clinical practice is based on case series (Dan et al., 2007; Ostergaard & Balslev, 2001; Shaaya et al., 2016; Thibert et al., 2009). The ACDs likely to provide benefit with limited adverse effects include clobazam, levetiracetam, and clonazepam (Figure 2). The consensus recommendation is to treat with clobazam or levetiracetam as first line therapy and to consider dietary intervention, including a ketogenic diet (KD) (Evangeliou et al., 2010; Groesbeck et al., 2006) or low glycemic index therapy (LGIT)(Grocott et al., 2017; Shaaya et al., 2016; Thibert et al., 2012). KD is recommended for infants and children with feeding tubes, whereas for other children, LGIT is recommended as first-line dietary therapy. If not completely effective, LGIT is converted to KD. Failure to control seizures with two medications warrants referral to an epileptologist. Since generalized seizures are prominent, broad spectrum ACDs are recommended. Phenobarbital, primidone, carbamazepine, phenytoin, and vigabatrin are contraindicated (Nolt et al., 2003). Parental reports of the effects of various forms of artisanal cannabidiol (CBD) for epilepsy are promising (unpublished); there is now an FDA-approved CBD medication (Epidiolex). Although little evidence exists, this is a promising medication for seizures, and it may help NEM. The high rate of motor side effects caused by valproic acid indicates sparing use unless as a bridge medication or failure of other ACDs and diet (Shaaya et al., 2016). AS individuals should receive a prescription for a rescue medication such as rectal diazepam gel or intranasal midazolam for prolonged seizures. Interruption therapy for episodes of NCSE with diazepam divided 2–3 times daily with a taper over 5–7 days has benefit (Worden et al., 2018).

Seizure alarm devices may be considered but are not particularly helpful for subtle seizure types such as atonic and atypical absence seizures. Caregivers should be educated on seizure management, particularly on the recognition of NCSE. Some with AS are able to come off of ACDs eventually, but there are no clear guidelines. While ~65% of adults will become seizure-free, many adolescents and adults will stay on ACDs, such as clobazam and clonazepam, to treat symptoms like sleep, anxiety, and NEM.

3.3 | Gastrointestinal (Table S2)

3.3.1 | GERD/Vomiting

GERD is common and may persist or recur in adulthood (Bindels-de Heus et al., 2020; Glassman et al., 2017).

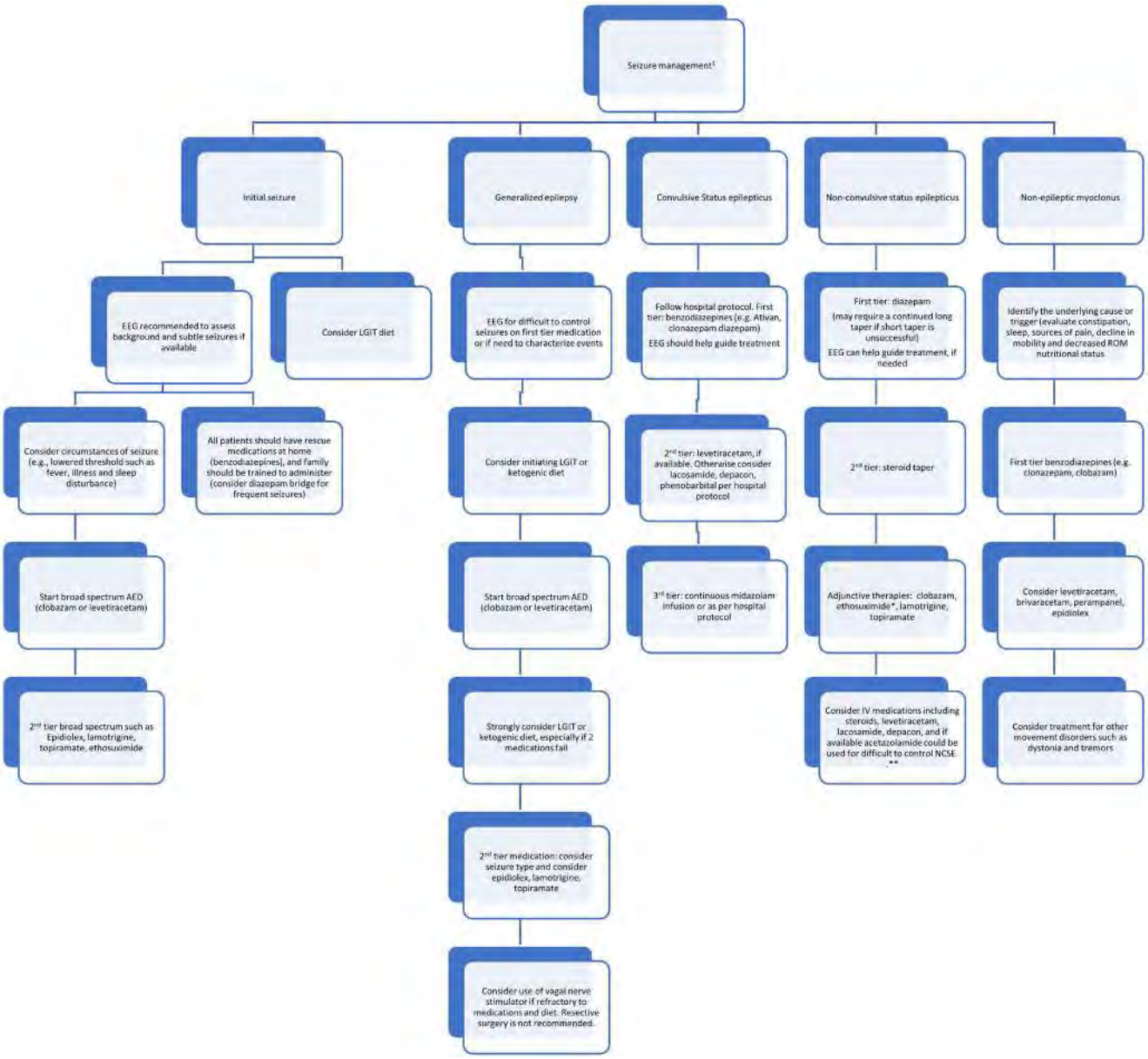

FIGURE 2 Management Algorithm for Seizures in Angelman Syndrome (AS). 1 Ask all patients about drug allergies. * Avoid phenytoin and phenobarbital for NCSE. All patients should have an emergency plan for management of seizures. Abbreviation ACD anticonvulsant drug; EEG electroencephalogram; LGIT low glycemic index therapy; NCSE nonconvulsive status epilepticus.

Signs include gagging, frequent swallowing, and pain or discomfort during and after feeding. In infants, therapy often starts with feeding in an upright position and keeping the child in this position for at least 30 mins post-feeding. Adjustments in posture (e.g. side lying position), technique, and formula are helpful. Consideration should be given to thickening feeds and dietary modifications. Referral for intensive feeding therapy is recommended. Uncontrolled GERD may cause esophagitis and upper GI bleeding. In older individuals, vomiting can be a sign of gastroparesis. Back arching, poor sleep, gagging, regurgitation of food, and unexplained discomfort should prompt a trial of a proton pump inhibitor or H2 blocker. Prokinetic medication may treat refractory symptoms. Causes of vomiting include severe constipation, migraine variants, rumination, urinary tract infection, medication side effects, and anxiety. In some, vomiting becomes behavioral.

3.3.2 | Constipation

The prevalence of constipation is 80% and requires treatment (Bindels-de Heus et al., 2020; Glassman et al., 2017). Constipation may contribute to increased seizures, sleep disturbance, and behavioral changes.

The workup includes evaluation of fluid and fiber intake and adding dietary fiber when appropriate. Adding magnesium, probiotics, or medium-chain triglyceride oil to the diet may help. Stool softeners are typically the next step after dietary changes, followed by stimulants. Refractory constipation may require intermittent or regular suppositories.

3.3.3 | Cyclic vomiting

Individuals may present with persistent vomiting episodes with serial vomiting and intervening symptom-free periods (Glassman et al., 2017). This is distressing and often results in dehydration. The etiology may be a migraine variant, though anxiety and/or GERD may also play a role. In addition, allergies and/or acute illness causing congestion and post-nasal drip may result in persistent emesis that requires antiemetics and/or fluid resuscitation. Treatment for chronic migraines, including amitriptyline, cyproheptadine, and topiramate, or treatments for anxiety and GERD as needed may be beneficial.

3.3.4 | Hyperphagia

Hyperphagia defined as inability to recognize satiety and related behaviors is recognized (Bindels-de Heus et al., 2020; Carson et al., 2019; Fridman et al., 1998; Hanzlik et al., 2020; Kirkilionis et al., 1991). This may be characterized by an obsessive compulsive component and driven by times of anxiety, change in routine or transition in general. Those with uniparental disomy or ImpDs are at higher risk (Carson et al., 2019; Fridman et al., 1998). Management strategies include scheduled meal times with a visual schedule, the use of partitioned and smaller plates, and a diet with increased protein and decreased carbohydrates. Locking up food may be necessary. Food for rewards should be avoided. Prospective data from 100 parents of children with AS showed that 32% reported hyperphagia, varying from no intrinsic limit in eating to searching for food and eating nonfood items (Bindels-de Heus et al., 2020). Up to 50% of adults have hyperphagia. Elevated body mass index (BMI) was associated with hyperphagia (Bindels-de Heus et al., 2020).

3.3.5 | Food allergy and Eosinophilic Esophagitis

For children with difficult GI symptoms, food allergy testing should be considered. When allergy testing is negative, food sensitivities (e.g., dairy and gluten) may be present. An elimination diet, i.e., removing one food at a time for a short period (~2 weeks), may be helpful to identify the foods that worsen gas, bloating, and constipation. Some children with food allergies develop eosinophilic esophagitis (EoE), which typically requires an elimination diet and treatment with medications prescribed by gastroenterologists or allergists. In a case series from 2 clinics, 4% of 97 children with deletions or UPD had EoE, whereas none of the 23 children with mutations or ImpD had EoE (Glassman et al., 2017).

3.3.6 | Drooling

Drooling is caused by open-mouth behavior, less frequent swallowing, or problems associated with the oral phase of swallowing. Unless there is accompanying aspiration, there is no indication for therapy, but social acceptance is a concern. Use of bibs and absorbent wristbands for mouth wiping are usually adequate. Stimulation of mouth closure and active swallowing can be done. Anticholinergic therapies such as glycopyrrolate or sublingual administration of atropine eyedrops (Norderyd et al., 2017) or parotid botulinum toxin injections may be employed, but the adverse effect of reducing saliva on dental health should considered (Gonzalez et al., 2017; Moller et al., 2015; Nordgarden et al., 2012; Pena et al., 2009; Reid et al., 2013). Side effects, like constipation, dry eyes, and thickened sputum, may prohibit these treatments.

3.3.7 | Dietary therapy

Research is necessary to further elucidate the optimal recommendations for dietary management. KD and LGIT are indicated for refractory epilepsy, but may also have other benefits (Evangeliou et al., 2010; Grocott et al., 2017; Groesbeck et al., 2006; Shaaya et al., 2016; Thibert et al., 2012). The classic KD is calculated in a ratio of grams (g) of fat to g of protein plus carbohydrate combined with 90% of calories from fat (Bergqvist, 2012; Evangeliou et al., 2010; Kossoff et al., 2002, 2018; Kwiterovich et al., 2003). A 3:1 or lower ratio can be used to increase protein or carbohydrate intake and is appropriate for diet initiation (Table S5)(Kossoff et al., 2018).

LGIT allows liberalization of carbohydrate intake to 40–60 g/day but regulates the type of carbohydrates, favoring those that produce small changes in blood glucose (glycemic index <50). The main side effects of KD/LGITs are gastrointestinal disturbances, hyperlipidemia (temporary), metabolic acidosis, and occasional renal calculi (Bergqvist, 2012; Kossoff et al., 2018). Children

with treatment-resistant epilepsy are at a high risk for poor bone health due to prolonged ACD exposure, direct and indirect effects of ACDs on calcium and vitamin D metabolism, and motor impairments that affect weight-bearing. The combined effect of KD creating a high "acid load" via ketone bodies, alterations in vitamin D, and lowering of growth factors increases this risk (Bergqvist, 2012; Bergqvist et al., 2007, 2008). In the optimal clinical management recommendations of the KD Study Group, 48% of centers advocate screening with dual energy X-ray absorptiometry (DEXA) scan in children to evaluate for osteopenia when on the KD for >2 years (Kossoff et al., 2018). Supplementation with vitamin D, calcium, and B vitamins should be provided at the recommended daily allowance (Vestergaard & Sayegh, 1966). A multivitamin with minerals is a universal recommendation (Makris et al., 2018). Levels of carnitine, selenium, magnesium, zinc, phosphorus, iron, and copper should be monitored along with beta-hydroxybutyrate while on dietary therapy. Individuals with hyperphagia may benefit from more liberalized KDs such as Modified Atkins Diet or LGIT (Bindels-de Heus et al., 2020).

3.4 | Sleep

Sleep problems are present in up to 80% of individuals with AS (Williams, 2005), including problems with settling and insomnia, awakenings during the night, and early awakening. Besides a shorter sleep duration, sleep tends to be more fragmented (Bruni et al., 2004; Miano et al., 2004, 2005). Sleeping difficulties decrease with age, although many adolescents and adults continue to have disordered sleep and co-sleep (Walz et al., 2005).

Poor sleep quality and diminished amounts of REM sleep negatively impact the regulation of behavior and worsen seizures (Dosier et al., 2017). Changes in behavior should prompt consideration of new onset sleep disorders. Epilepsy, ACDs, GERD, scoliosis, and constipation can further negatively impact sleep (Bindels-de Heus et al., 2020). Individuals with AS should be screened for sleep problems and, if present, a detailed characterization of the sleep/wake schedule and routines should be investigated. Overnight polysomnography is indicated for individuals suspected of having sleep-related breathing problems, nocturnal seizures, or unusual behavior during sleep. Given anxiety in unfamiliar environments, polysomnography may be challenging. A sleep diary and actigraphy (Braam et al., 2008; Iii, 2015) are non-invasive means of characterizing sleep/wake patterns in the home environment. Video polysomnography may help to objectively observe sleep patterns.

For sleep disorders, treatment of contributing problems such as GERD, epilepsy, and behavioral issues including anxiety should be optimized. Specific sleep disorders such as obstructive sleep apnea (OSA) should be managed with the help of appropriate specialists. Sleep problems are initially treated with behavioral therapies and promoting sleep hygiene. Optimal sleep hygiene consists of a regular sleep-wake rhythm, a bedtime routine, and a bedroom that is calm, cool, and dark (Hylkema & Vlaskamp, 2009). Individuals with AS benefit greatly from safety beds and we often recommend early referral for an enclosed bed in planning for transition from the crib. Behavioral therapies often consist of managing parent-child interaction at night. Intensive coaching of parents can support behavioral interventions (Allen et al., 2013). Medicinal treatments targeting sleep difficulties are beneficial and often needed if behavioral therapies are ineffective. These include low-dose melatonin (Braam et al., 2008; Egan et al., 2020; Galvan-Manso et al., 2002; Paprocka et al., 2017; Takaesu et al., 2012; Zhdanova et al., 1999), alpha agonists (clonidine or guanfacine), benzodiazepines (clonazepam), gabapentin or pregabalin, antihistamines (promethazine or diphenhydramine), antidepressants (mirtazapine (Hanzlik et al., 2020) or trazodone), and in refractory cases antipsychotics (e.g. quetiapine (Wine et al., 2009), Figure 3).

3.5 | Cognitive and behavioral phenotypes

The neurodevelopmental profile of AS includes severe intellectual disability, global developmental delay, and lack of speech (Dagli et al., 2012). Studies have found significant delays across all domains, with cognitive skills trending below the 24–30 months developmental level, using the Bayley Scales of Infant Development (Gentile et al., 2010; Peters et al., 2004; Sahoo et al., 2007). Severity of cognitive delay correlates with molecular subtype (deletion is most severe), (Keute et al., 2020) but additional factors may contribute, such as underlying seizure control, selection of ACDs, access to habilitative therapies, and genetic background. Tables S2–S4 provide details of therapeutic interventions. At the time of delays, even prior to an official genetic diagnosis, referral to early interventional services for physical (PT), occupational (OT), and speech and language therapy (ST) are needed. Therapies should continue throughout life (Khan et al., 2019). Individuals with AS may benefit from alternative therapies in particular hydrotherapy especially due to their love of water. There is some evidence this improves behavior and social interaction in autism spectrum disorders (ASD) (Gueita-Rodriguez et al., 2021; Mortimer et al., 2014). In addition it improves functional mobility of infant and toddlers

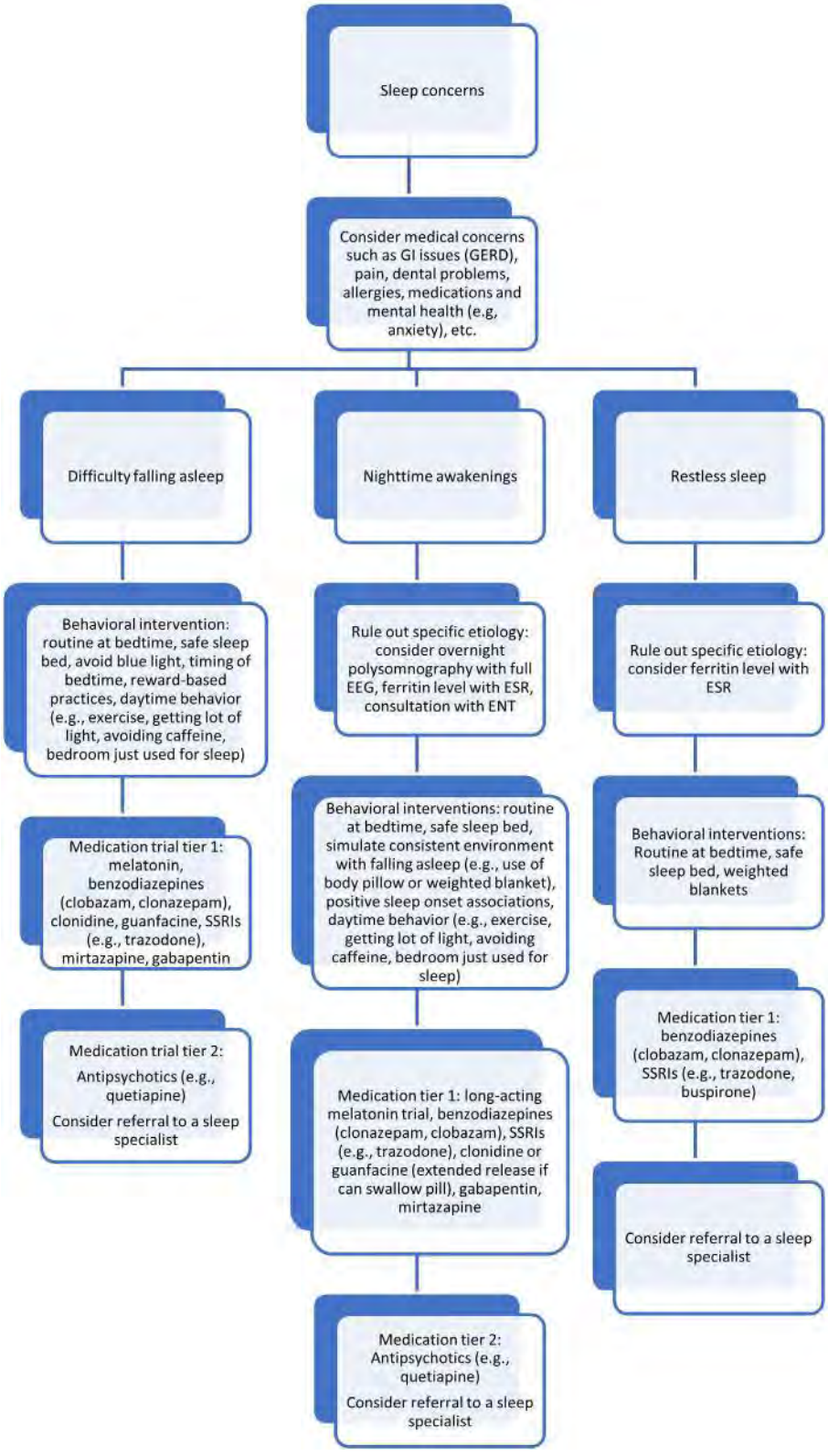

FIGURE 3 Management Algorithm for Sleep Disturbances in Angelman Syndrome (AS). Abbreviations: GI gastrointestinal; GERD gastroesophageal reflux disease, EEG electroencephalogram; ESR erythrocyte sedimentation rate; ENT otolaryngologist/ear, nose and throat specialist.

(McManus & Kotelchuck, 2007), although the literature is varied (Getz et al., 2006). Hippotherapy benefits gross motor function and functional performance in individuals with neurodevelopmental disabilities (Park et al., 2014). It has been associated with improved body balance and posture and may have benefits for overall core strength (Matusiak-Wieczorek et al., 2016). Little evidence-base is available to suggest short periods of intensive physiotherapy; however, anecdotally programs such as Strengthening Program of Intensive Developmental Exercises and Activities for Reaching Maximal Potential or SPIDER therapy may be beneficial. More studies are required to recommend this to individuals with AS.

Frequent smiling and laughing resulting in an apparent happy disposition are hallmarks (Williams et al., 2006). Laughter may increase markedly with anxiety and some patients appear discomforted during pervasive bouts of laughter. Although rare, life-threatening laughter is amenable to pharmacological treatment (Vanagt et al., 2005). Hyperactivity or hypermotoric behavior is consistently reported (Buntinx et al., 1995; Galvan-Manso et al., 2002; Zori et al., 1992). Impulsivity is consistent with the level of intellectual disability (Barry et al., 2005). High rates of disruptive behaviors are reported (Arron et al., 2011; Larson et al., 2015; Sadhwani et al., 2019) during periods of excitement, while attempting to avoid nonpreferred tasks, or when seeking to maintain a caregiver's attention (Strachan et al., 2009). Such behaviors often appear to have communicative intent and may be triggered by internal states such as pain, fatigue, anxiety, or a preference for specific sensory input. A recent study using a modified anxiety questionnaire in 100 caregivers found high levels of distress with separation (Wheeler et al., 2019), which was lowest in individuals with a deletion subtype.

Individuals with AS have many features of ASDs such as repetitive behaviors and restricted/obsessive interests. This can include repetitive chewing/mouthing and stereotyped hand and body movements (Moss & Howlin, 2009). Sometimes, these movements are used to focus on a task or to reduce stimuli from the environment. Individuals with AS often respond to ABA therapy and referral is recommended for maladaptive behaviors and ASD features.

New onset behavioral concerns or changes in sleep habits should prompt a thorough exploration for unrecognized medical illness/infection, constipation, dysmenorrhea, esophageal reflux, dental problems, scoliosis or post-ictal confusion/sedation. Behavioral therapies, such as ABA, along with the use of an augmentative and assistive communication (AAC) device, should play an important role in the understanding and treatment of behavioral concerns, including reduction of problem behaviors and development of adaptive skills (Summers, 2012). Medication management is often needed (Figure 4).

Educators may have limited knowledge of AS. Developing an appropriate individualized education plan (IEP) capitalizing on the person's social skills while focusing on individualized 1:1 learning and instruction is critical to maximize educational potential as well as to improve communication and motor skills. Consistent with the Individuals with Disabilities Education Act, education should take place in the least restrictive environment. For some children with AS this might be in an integrated classroom alongside typically developing children, while for others it may be in a self-contained classroom, or a combination of the two. Decisions about appropriate school/classroom placement should be arrived at through shared decision-making between the school and family. Some individuals, particularly of the mosaic subtype achieve the ability to read and write to some degree (Hanzlik et al., 2020). The IEP should include intensive PT, OT, and ST (Table S2–S4). Parents, teachers, and caregivers should be trained and supported in the use of the AAC device with carryover from school to the home environment. If a child has behavioral challenges, as part of the IEP, families can request a functional behavioral assessment to assess for triggers and develop a management plan (Williams et al., 2006). A thorough AAC evaluation includes trials of at least 3 different AAC systems to effectively select the best device for the individual.

3.6 | Ophthalmology (Table S2)

Evaluation by ophthalmology is recommended at diagnosis and annually (Dickinson et al., 1990). Strabismus is common (Khan et al., 2019; Michieletto et al., 2011; Williams, 2005). Conservative measures such as patching or corrective lenses are often difficult to implement because of an inability to cooperate with the treatment. Thirty percent of persons require strabismus surgery (Khan et al., 2019). In two small case series, persons with large angle exotropia showed excellent 6-month post-operative alignment after bilateral lateral rectus recessions (Mah et al., 2000; Ye et al., 2019).

Astigmatism is the most common refractive error. Almost all patients in an Italian study as well as 2 smaller series exhibited at least 1 diopter, with more than half showing potentially amblyogenic levels of astigmatism (>2 diopters) (Michieletto et al., 2011; Ye et al., 2019). While keratoconus has been described in adults, it is unclear whether this finding is associated with childhood astigmatism or behavioral eye rubbing (Larson et al., 2015). Further, in the Italian study, greater than 1 diopter of hyperopia or myopia was seen in 76% and 9% of the individuals, respectively (Michieletto et al., 2011). Thus, the majority of these children fit the general criteria for

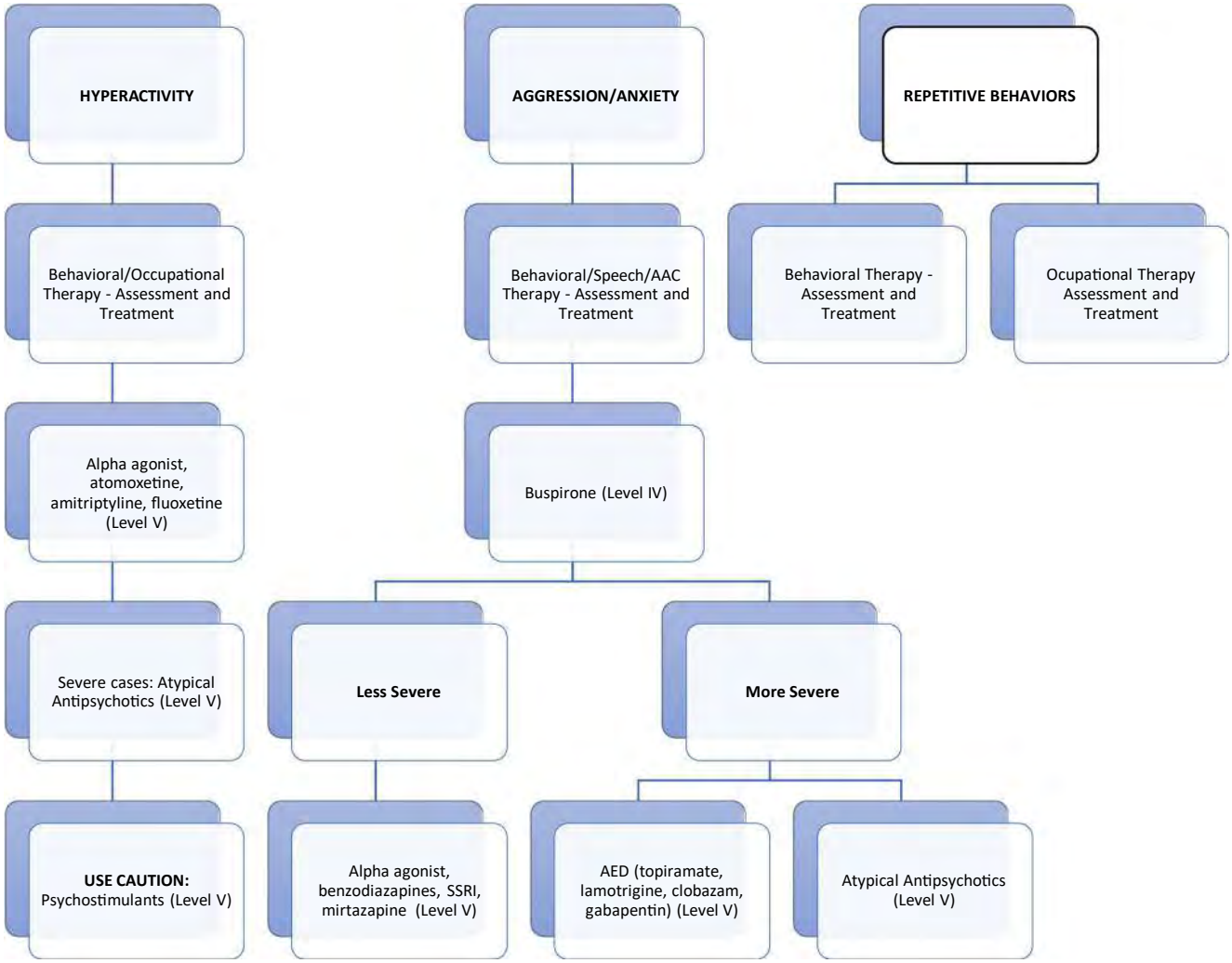

FIGURE 4 Management Algorithm for Behavior in Angelman Syndrome (AS). Abbreviation ACD anticonvulsant drug; AAC assistive and augmentative communication device; SSRI selective serotonin reuptake inhibitor.

corrective lenses; however, tolerance of glasses is low, and rates of amblyopia have not been reported.

Assessment is often based on ophthalmic findings and visual behavior. In the literature, some individuals with AS have severe ophthalmic pathology such as optic and chorioretinal atrophy accounting for poor visual function (Rufa et al., 2003; Van Splunder et al., 2003). Clinically one of the first symptoms may be cortical visual impairment that improves with time (Micheletti et al., 2016). There is a wide spectrum of characteristics in cortical visual impairment that ranges from complete blindness to altered visual perception. Nystagmus has been reported in 11% of patients with cortical visual impairment (Huo et al., 1999). Consistent with this, 9% of individuals with AS exhibited nystagmus (Michieletto et al., 2011). Referral for OT/PT and vision/mobility services to maximize visual function is critical.

Oculocutaneous albinism due to a mutation in the *OCA2* gene located on the paternal copy of chromosome 15 should be considered in individuals with AS who have congenital nystagmus, iris hypopigmentation and translucency, reduced pigmentation of the retinal pigment epithelium, and foveal hypoplasia.. Identification of children with oculocutaneous albinism due to a deletion on chromosome 15 and a mutation on the other allele is important due to changes in management including regular use of sunscreen, management of low vision, regular ophthalmology follow up, and cancer screening.

3.7 | Orthopedics

Lower bone density may occur in individuals with developmental delay compared to neurotypical individuals. Use of anti-epileptic drugs and KD, immobility, decreased exposure to sunlight and late puberty are negative influencing factors (Srikanth et al., 2011). Low-impact fractures may occur as a result. DEXA scan is recommended

to assess bone health every 2 years depending on risk factors such as KD, non-ambulatory individuals, ketogenic diet, history of >2 fractures without clear trauma, and age of onset of puberty. In females >65 years old screening should be implemented yearly. Vitamin D supplementation, stimulating daily physical activity (especially with vertical positioning), and 15–30 min of sunlight exposure/day are advised (Lin et al., 2015).

Hip dysplasia may occur due to external rotation of the legs along with decreased tone and delayed ambulation. Standard hip screening and radiographs in the frog leg position, particularly in non-ambulatory children, should be performed, with orthopedic referral when indicated. Early PT is recommended to maintain or improve range of motion. The use of standers assist in increasing bone density.

At least 80% of children will achieve independent ambulation with an average age of onset of 3.7 years old for those with deletions (Williams et al., 2010). The gait pattern is associated with reduced step length versus cadence and continues throughout childhood despite adjustment for delayed ambulation onset (Grieco et al., 2018). Gait pattern and mobility change as individuals age; however, the commonly reported spasticity including dynamic contracture is not well characterized. Initial treatment should consist of PT and bracing to maintain range of motion and prevent static contractures. Gait analysis is recommended when considering orthopedic intervention, as many patients will develop maladaptive gait patterns which may worsen with inappropriate lengthening procedures (Larson et al., 2015). Larson reported that 10% of persons underwent tendon lengthening with varying results. Based on clinical observation, many patients develop limited ankle dorsiflexion with compensatory foot pronation and instability. This presentation can lead to a flexed knee gait pattern which is distinguished from a classic crouch gait in that passive ankle dorsiflexion is limited rather than excessive and accompanied by compensatory ankle pronation. In a sample of individuals, 62% presented with subluxed or pronated ankles (Williams et al., 2010; Zori et al., 1992), which can be treated with orthotics. If there is significant fixed angular deformity, corrective osteotomy remains controversial as recovery post-procedure is often poor. Anecdotally, botulinum toxin injections may worsen gait and should be approached with caution due to the risk of exacerbating weakness and contributing to progression of a flexed knee gait pattern.

The incidence of scoliosis in children with AS is 10–30% (Smith, 2001; Zori et al., 1992) and in adults is 30–70% (Buntinx et al., 1995; Laan et al., 1996; Prasad et al., 2018). Most curves are thoracic, but up to 20% have increased lumbar lordosis associated with trunk weakness, increased anterior pelvic tilt, and crouch gait (Beckung et al., 2004). In adults, one study reported 21/22 patients had curves greater than 40 degrees (Guerrini et al., 2003). Standard screening with the forward bend test is appropriate for ambulatory patients, as well as orthopedic referral with radiographic monitoring. Curve assessment and treatment algorithms should follow those for typically developing children (Sewell et al., 2016). In non-ambulatory patients, earlier use of thoracolumbosacral orthoses (TLSO) should be considered for promoting bimanual manipulation and social interaction. There are conflicting data regarding an association between ambulatory status and scoliosis progression, but there appears to be a female predominance (Laan et al., 1996; Larson et al., 2015; Smith, 2001). Continued monitoring of curve progression and effect on cardiopulmonary function and quality of life should guide intervention. There is only one study that has evaluated the benefit of surgical intervention for scoliosis (Sewell et al., 2016). While there was a small but significant absolute improvement in patient reported quality of life in the surgical group, there was a 60% complication rate. While this does not negate the indication for surgical treatment, frank preoperative risk-benefit discussions should occur.

Orthopedic concerns as individuals with AS transition to adulthood include preserving range of motion and managing body weight. It is reported that over time hip and knee flexion contractures, scoliosis, and decreased stamina develop (Grieco et al., 2018). However, 64–75% of all adults with AS are able to walk independently. Plantar flexion contractures may also develop. By 13 years of age, up to 25% of AS patients will develop significant gait abnormalities which share features of crouch gait (Bindels-de Heus et al., 2020). PT may be needed intermittently throughout life to address changes in function, gait, posture, range of motion, and strength (Table S3).

3.8 | Clinical trials

Published clinical trials with negative results include: levodopa (Tan et al., 2018), minocycline (Grieco et al., 2014; Ruiz-Antoran et al., 2018), and folic acid and betaine (Han et al., 2019; Keute et al., 2020; Peters et al., 2004, 2010) and betaine, metafolin, creatine, and vitamin B(12) (Bird et al., 2011). A phase 3 trial of gaboxadol (OV101) in children recently reported negative results (NCT04106557), despite promising phase 2 results in an adolescent and adult population (Bird et al., 2021). An exogenous ketone trial (Herber et al., 2020) recently showed safety and tolerability, improved stool consistency and a trend toward other benefits (Carson et al., 2021, NCT03644693). Phase I/II trials of antisense oligonucleotide therapies to activate the paternal copy of *UBE3A* are underway (NCT04428281, NCT04259281).

3.9 | Adults with AS and transition of care

Adults have unique challenges: decline in mobility and a more sedentary lifestyle, NEM, GERD, constipation, anxiety, and behavioral concerns. Sleep, seizures, and hyperactivity may improve (Laan et al., 1996; Larson et al., 2015; Pelc et al., 2008). Transition to adulthood requires consideration of ongoing educational and therapeutic supports including access to behavioral therapy such as ABA and AAC device support, applying for disability, state-specific waiver programs, and guardianship. An extensive IEP planning meeting should be done at 15–16 years old. There are several excellent resources such as https://www.gottransition.org/. Early planning includes use of community support resources (ARC and NORD) and patient support organizations (Foundation for Angelman Syndrome Therapeutics (FAST) and Angelman Syndrome Foundations (ASF)). Financial planning is critical and may include a special needs trust for the AS child/adult. Enrollment in vocational/recreational opportunities including adaptive sports or vocational training programs should be considered early. Utilization of transition clinics or the ASF clinical network for scheduled transition visits is advised. Preventive healthcare under anesthesia at generally recommended intervals is recommended.

3.10 | Caregiver and family health

Caregivers are at high risk for experiencing negative consequences. Continued translationally oriented research is crucial to understand the specific needs of caregivers across the lifespan. Clinical specialists and providers should be aware that stressors are associated with caregiving, including negative impacts on social networks, family dynamics, and financial security, which lead to or exacerbate mental health and physical health challenges for caregivers. Providers can offer much needed relief such as respite care, which in turn can have long-term positive impacts on the individual with AS and their support system as a whole (Adams et al., 2018; Bailey et al., 2009; Blucker et al., 2011; Buelow et al., 2006; Camfield et al., 2016; Didden et al., 2004; Falk et al., 2014; Miodrag & Peters, 2015; Murphy et al., 2007). The relationship of siblings is unique and requires family-based approaches (Love et al., 2012). Regular individualized attention to siblings as an outlet to share concerns and challenges is important. Referral to support groups locally and nationally (FAST and ASF) with connection to other families is key to create support networks. Tools for siblings may include children's books and support groups.

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AUTHORS' CONTRIBUTIONS

JD worked with AA to Chair the Steering Committee, develop the methods, invited the chairs of the committees, and provided oversight of the project. JD and her team completed the systematic review of the literature with input from 2 reviewers. JD compiled the final version of the manuscript, edited, and revised the manuscript. She was the chair of the Genetics Committee and completed meetings with the group. She attended group meetings of the other committees. MN drafted, edited, and revised the neurology section and served as a member of the Neurology Committee. JS served on the Behavioral Committee and edited the manuscript. LB edited and revised the manuscript. She provided mentorship for the Genetics Committee. KGCBB chaired the General Health Committee and revised and edited the manuscript. MJV was part of the General Health Committee and revised and edited the manuscript. MYDW edited and revised the manuscript and assisted with the Neurology and Sleep Committees. CN served on the Speech and Language Development Committee and revised and edited the accompanying section. MTHR chaired the Sleep Committee and revised and edited the manuscript. BMVIK served on the Physical Therapy Committee and edited and revised the accompanying section. SE chaired the Reproductive Health Committee and revised and edited the manuscript. MD served on the Reproductive Health Committee and revised and edited the manuscript. TK chaired the Toileting Committee. GDM and AK served on the Nutrition Committee and revised and edited the accompanying section. SN served on the Neurology Committee and revised and edited the manuscript. RT served on the Neurology Committee and revised and edited the manuscript. He met with JD and AA to review the final version. DG edited and revised the Sleep section of the manuscript. CK chaired the Behavioral Health Committee. He edited and revised the manuscript. KP and NS served on the Behavioral Health Committee and edited and revised the manuscript. AS Chaired the Development Committee and revised and edited the manuscript. HH edited and revised the manuscript. AW chaired the Caregiver Health Committee and revised and edited the manuscript. CW served on the Speech and Language Development Committee and revised and edited the accompanying section. MD chaired the Speech and Language Development Committee and revised and edited this section. AT chaired the Occupational Therapy Committee and revised and edited this section. EK and LD served on the Occupational Therapy Committee and revised and edited this section.

KK chaired the Physical Therapy Committee and revised and edited the accompanying section. KA, CB, and NH served on the Physical Therapy Committee and revised and edited the accompanying section. JPG served on the Ophthalmology Committee and revised and edited the accompanying section. BLB chaired the Ophthalmology Committee and revised and edited this section. RCC served on the Orthopedics Committee and revised and edited this section. SH provided support to AA and revised and edited the manuscript. HGC chaired the Orthopedics Committee and revised and edited the accompanying section. KO served on the Caregiver Committee and revised and edited the accompanying section. ERJ served on the Steering Committee as a representative from the Angelman Syndrome Foundation and parent advocate and revised and edited the manuscript. AB served on the Steering Committee as a representative from the Foundation for Angelman Syndrome Therapeutics and parent advocate and revised and edited the manuscript. CAB served on the Genetic Committee and revised and edited the manuscript. CW served as a mentor to JD for the Genetics Committee and revised and edited the manuscript. AA was awarded funding through the Million Dollar Bike Ride. She served as part of the Neurology Committee.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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SEIZURE TREATMENT GUIDELINES

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To Whom it May Concern:

This individual has been diagnosed with a rare neurogenetic disorder called Angelman syndrome (AS). AS is caused by a loss of the maternally expressed UBE3A gene. This is most commonly due to a deletion of the Angelman critical region on the maternal copy of chromosome 15q11.2-13.1, but there are other genetic mechanisms as well. ***Individuals with Angelman syndrome are at high risk of developing seizures, particularly in the setting of febrile illnesses in childhood.*** As many as 85-90% of children with AS will develop seizures by 3 years old. Children with Angelman syndrome often present with atonic or drop seizures but can have generalized tonic-clonic, focal or other seizure types as well. This letter is meant to provide general guidelines for treatment of seizures in Angelman syndrome, however each child is unique and may not respond to the typical medications used in AS.

Prolonged seizures or not returning to baseline between brief seizures:
Benzodiazepines work very well for stopping seizures in individuals with Angelman syndrome and should be considered first line. Depending on clinical status, oral versus IV or intranasal preparations can be utilized and in the typically recommended weight based dosing for children and standard dosing for adults.

Usually effective & well tolerated initial daily medications for outpatient management of new onset seizures:
Levetiracetam (Keppra)
Clobazam (Onfi)

Less desired medications: Valproate (aka Depakote, Depakene, valproic acid)
In a large series, "patients on valproic acid therapy exhibited increased tremor, decreased balance and/or regression of motor skills, which resolved after tapering off of this medication" (Thibert, Epilepsy Behavior 2016)

All patients with Angelman syndrome who have had a first time seizure should be provided with a prescription for seizure rescue medications which can include rectal diazepam (Diastat), intranasal diazepam (Valtoco approved for 6yo and older in 2020), intranasal midazolam (any form and Nayzilam is approved for 12yo and older) and in some countries buccal midazolam products are available for rescue therapy.

It is important to recognize that this is a rare genetic syndrome and often times parents are the first to recognize clinical decline in their children and should be taken seriously when concerned for seizures as they are so pervasive in this condition. Delay in treatment can lead to development of nonconvulsive status epilepticus (NCSE), which can often be managed as an outpatient as well. Please see attached guidelines for outpatient management of NCSE as adapted from the extensive experience of the Angelman team at Massachusetts General Hospital. For urgent consultation with a neurologist who specializes in the management of seizures in Angelman syndrome, please email clinics@angelman.org. This email is monitored daily between 8AM - 8PM and we are happy to facilitate expert consultation in a timely manner. (Coming soon a 24 hour seizure hotline that can be used to consult with AS expert).*

LADDER Learning Network
angelman.org/clinics

Angelman Syndrome Foundation
angelman.org

MANAGEMENT OF NONCONVULSIVE STATUS EPILEPTICUS IN ANGELMAN SYNDROME

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Management of Nonconvulsive Status Epilepticus in Angelman Syndrome

Up to 50% of patients with Angelman syndrome (AS) will have nonconvulsive status epilepticus (NCSE) with myoclonic or atypical absence status. Adapted from the experience of the Angelman group at Massachusetts General Hospital, this document provides guidance on the outpatient management of patients with AS and NCSE treating
with a tapering course of oral diazepam.

While standard clinical EEG can confirm the presence of nonconvulsive status epilepticus (NCSE) in individuals with Angelman syndrome, it is not always necessary.

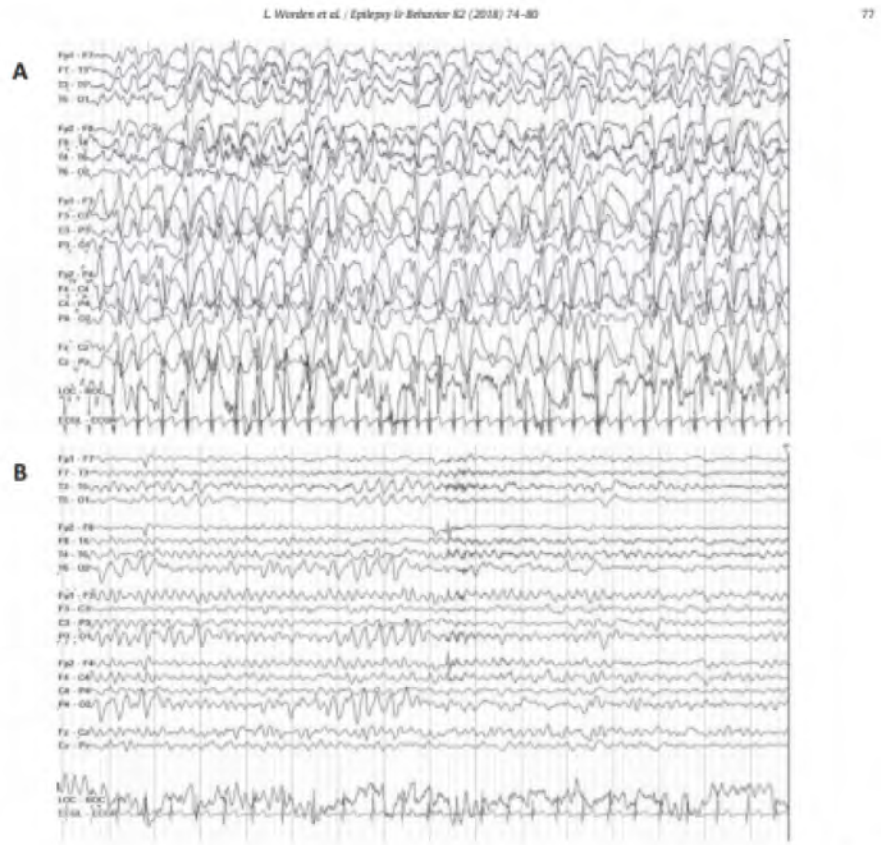

Fig. 2. Electroencephalogram sample for Patient 1 during 3rd episode of NCSE. A. Prediazepam treatment EEG showing 2–2.5 Hz, 700 μV frontally predominant generalized spike–wave activity. B. Postdiazepam treatment EEG showing continuous diffuse irregular 5–6 Hz, 200 μV theta slowing and occasional biposterior notched delta activity.

NSCE should be suspected with the following constellation of clinical findings:

- Somnolence
- Fatigue
- Regression
- Increased seizure activity*
- Cluster of seizure activity at onset*
- Decreased activity

Angelman syndrome is a rare genetic disorder and caregivers are often the first to recognize the signs of clinical decline in their child. Their concerns should be heeded and low threshold to consider valium taper if NCSE is confirmed or suspected.

Recommended Valium Taper Regimen:

6 day tapering course of oral diazepam (lorazepam can be used if there is a tolerance issue or sensitivity to diazepam)
Beginning with 0.25-0.5 mg/kg/day divided TID x 2 days
Then tapering to BID dosing for 2 days and then daily for 2 days before tapering off entirely

Example schedule for 20kg child:

0.3mg/kg/day = 6mg/day

DAY 1-2	2MG TAB TID
DAY 3-4	2MG TAB BID
DAY 5-6	2MG TAB DAILY
DAY 7	OFF VALIUM, BACK TO BASELINE MAINTENANCE MEDICATIONS

In addition, consider increasing maintenance dosing of medications or further carb restriction for children on diet therapy for seizure control to prevent future breakthrough seizures and/or recurrent NCSE.

Some children required repeat tapers or prolonged courses up to 2 weeks to break NCSE.

Full reference: Worden L, Grocott O, Tourjee A, Chan F, Thibert R. Diazepam for outpatient treatment of nonconvulsive status epilepticus in pediatric patients with Angelman syndrome. Epilepsy Behav. 2018 May;82:74-80. doi: 10.1016/j.yebeh.2018.02.027. Epub 2018 Mar 27. PMID: 29597185.

Disclaimer:This document was created and reviewed by the 15q Clinical Research Network clinicians. This should not be considered medical advice, but a resource that you can provide to your medical care teams to help understand seizure activity and treatment options in Angelman Syndrome.

GENERAL ANESTHESIA BEST PRACTICES

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Preparing Your Child with Angelman Syndrome for General Anesthesia

General anesthesia, also sometimes called a general anesthetic or GA, is where a mixture of medicines is given to your child to keep them in a carefully controlled unconscious state, or 'sleep.' General anesthesia is used mainly for surgery, although in some circumstances your child may require a general anesthetic for some non-surgical procedures that require them to hold still for long periods of time, such as dental work, imaging (MRIs or CT scans), and lumbar punctures.

Children with Angelman Syndrome are special not only because they communicate differently, but also because they have medical issues and often take medications that may impact anesthesia, surgery and recovery. They may also require general anesthesia for some non-surgical procedures that other children can safely have without anesthesia. It is important to know that anesthesia for children with Angelman Syndrome is very safe, and the risk of anesthesia to your child is generally no different than a child without Angelman Syndrome.

When your child has a procedure requiring general anesthesia, they will be cared for by an anesthesiologist. An anesthesiologist, sometimes called an anesthetist, is a doctor that specializes in giving your child general anesthesia medicines and monitors your child closely during the surgery. In some instances, your anesthesiologist might be working with a certified nurse anesthetist (CRNA), who is also highly trained in anesthesia. When your child receives anesthesia, there will always be an anesthesiologist or a CRNA with them to keep them safe.

Before your child receives general anesthesia, it is important to communicate with your anesthesiologist and let them know that your child has Angelman Syndrome. By sharing your child's medical history, you can help the anesthesiologist take the best care of your child.

Fasting

Your child will need to fast before their surgery. Fasting before surgery is important to ensure that your child has an empty stomach when under a general anesthetic. Anesthesia medicines reduce a child's cough or gag reflex. If there is anything in the stomach when a child is having general anesthesia, there is a risk of food or liquid being breathed into the lungs and causing pneumonia. This is called aspiration. An empty stomach before anesthesia is always preferred. But, if your child requires an emergency surgery and they have not fasted, there are precautions that the anesthesiologist can take to reduce the risk of aspiration.

Different foods and drinks require different fasting times. Always check with your doctor about when to have your child stop eating and drinking before general anesthesia. This is very important, as there is a chance your child's surgery may be postponed if they are not adequately fasted. Fasting includes:

- Foods and fluids (including breast milk) – although the timing of fasting differs depending on the food or the fluid
- Oral and PEG (Percutaneous Endoscopic Gastrostomy) tube feeds
- Sweets / Lollies / Chewing Gum

One exception to fasting is medication. As a general rule, your child should continue taking their regular medications at the usual time unless otherwise requested by your doctor or nurse. Medications can be taken with a sip of clear liquid (if in tablet or powder form). Some specific medication-related issues to discuss with your doctor include:

- Medications that can interfere with surgery or procedures. These include medications such as blood thinners (aspirin / warfarin) or medicines for diabetes (insulin). Some medicines might need to be stopped prior to surgery.
- If the medication is a large volume of liquid
- If your child can only take medication hidden in food or fluids such as juice or applesauce

Before Surgery

Your child's anesthesiologist will:

- Ask you questions about your child's medical history
- Ask about any prior issues with anesthesia for your child or your family members
- Explain the plan for your child during the surgery or procedure
- Answer any questions you may have about anesthesia

Specific issues that the anesthesiologist may want to know include:

- Your child's seizure history and control, and anti-seizure medication
- A history of gastro-esophageal reflux disease (GERD), and how well-controlled it is
- Medications and drug / food allergies
- The level your child communicates at – this can include how they communicate pain and distress, and the best methods to communicate with your child, including the use of Augmentative and Alternative Communication (AAC) devices. This will be especially helpful for the nursing staff in recovery when your child wakes up.
- Safety measures and your child's mobility – medical staff may assume (especially for older children and adults) that your child can be left on a hospital bed without supervision, which may lead to your child accidentally injuring themselves.

Some children will be given a medicine to help them relax before surgery – this is called a premedication, and may be called a 'premed'. A premed may be given 15-60 minutes before surgery, but it is not essential for the anesthetic. If your child spits out the premed or is not keen on taking it, let your anesthesiologist know.

During Surgery

Children can go to sleep for procedures by one of two ways – your anesthesiologist will talk to you about the best and safest way for your child to have general anesthesia.

Option 1: Medicine through a drip

- This is where an IV is put into a vein
- A local anesthetic cream may be applied to numb some areas of the skin where an IV is put in
- This cream can take 45-90 minutes to work and will reduce the discomfort associated with having a drip inserted
- The anesthesia medicine is given into this IV
- It takes seconds to go to sleep with this medicine

Option 2: Breathing medicine through a face mask

- Some children go to sleep with a vapor (gas) medicine given to them with a mask that is placed over the mouth and nose
- Your child will breathe in a mixture of anesthetic gases that may smell funny but not unpleasant
- It takes a minute or two to go to sleep with this method
- It is normal for your child to wriggle, cough, breathe noisily or snore as they go to sleep

When your child is asleep, the anesthesiologist will insert a breathing tube. This breathing tube will allow the child to continue to breathe the anesthesia gases and remain asleep throughout the procedure.

After Surgery

The breathing tube is removed at the end of the surgery in the operating theatre or sometimes in the post-anesthesia care unit (PACU, also called recovery). Your child probably will not remember this tube coming out, but may have a sore throat or a croaky voice for a few hours after. The nurses will call you a little while after your child has arrived in recovery so you can be with your child as they wake up.

Depending on the surgery or procedure, it may take from a day up to a few weeks for your child to recover. Your child may need rest, and you may notice a change in your child's behavior pattern. Your doctor will let you know how long your child will need to rest at home, and how long it might take for your child to return to normal activities.

Key Points to Remember:

- General anesthesia or GA is a mixture of medicines given to your child to keep them asleep during surgery
- Your child will need to fast from food and fluid, but not medication, before surgery. Different foods and fluids require different fasting times, so always check with your doctor for specific instructions.
- Children can go to sleep for surgery by two ways – medicine can be given through an IV or gas can be breathed through a mask
- When your child has general anesthesia, they will never be alone – there will always be an anesthesiologist and/or CRNA with them
- Anesthesia for children with Angelman Syndrome is generally very safe

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MYOCLONUS IN ANGELMAN SYNDROME

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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 status, and electroencephalographs show interictal generalized spike and wave activity. Nonepileptic myoclonus occurred in 40% of individuals over 10 years of age, and prevalence appears to increase with age. The episodes of nonepileptic myoclonus arise during 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 nonprogressive 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

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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

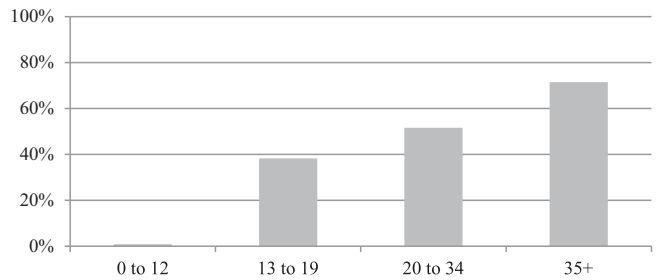

Fig. 1. Percent of patients with NEM by age group (n = 185).

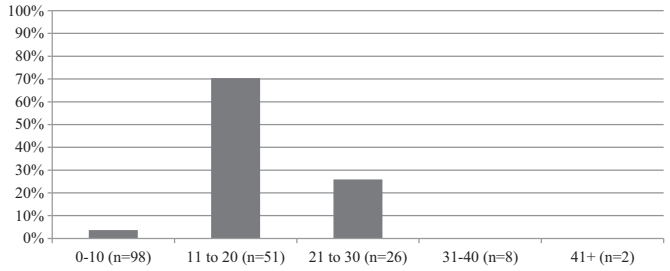

Fig. 2. Age of NEM onset by age group (n = 27).

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 events 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.

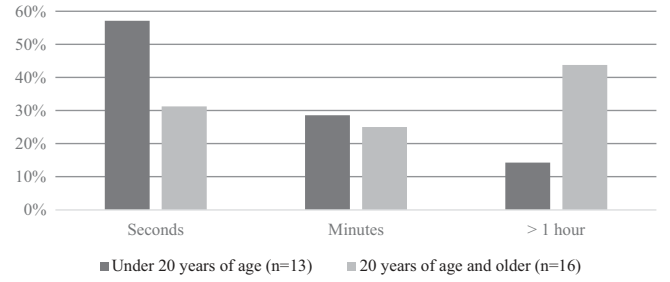

Fig. 3. Duration of NEM episodes by age group.

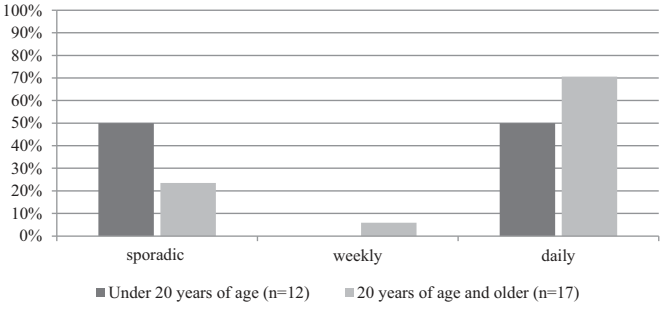

Fig. 4. Frequency of NEM episodes by age group.

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 lorazepam (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.

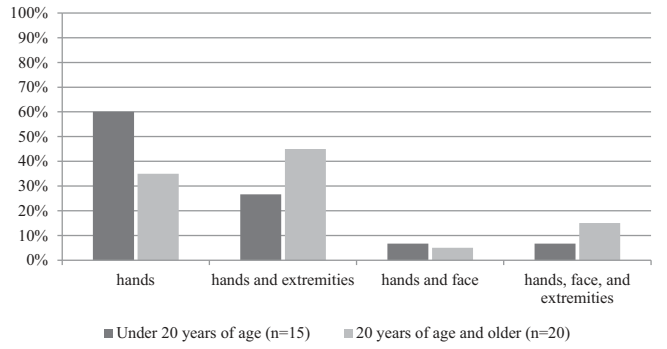

Fig. 5. Part of the body affected by NEM by age group.

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 these 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, lacosamide, 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

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.

Acknowledgments

We would like to acknowledge all of the families who have visited the Angelman Syndrome Clinic at Massachusetts General Hospital and the Lurie Center for Autism.

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PHYSICAL THERAPY AND OCCUPATIONAL THERAPY BEST PRACTICES

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Physical and Occupational Therapy Best Practices, Tips & Tricks, Equipment and Resources for those living with Angelman syndrome

This resource was created by a group of certified physical and occupational therapists that have a history of working with individuals with AS. This document is intended to be a support document that you can take to your team to support their efforts with your individual with AS. If your PT or OT would like to talk with anyone from this team for support, please have them reach out to info@angelman.org. Please note that this is NOT a complete list or a standard of care for AS, but a resource created by passionate individuals experienced in this area.

BEST PRACTICES

There are many theoretical approaches to physical therapy e.g., neurodevelopmental, activity based, systems theory, dynamic systems. Most therapists, I hope, would support exploration (a mix of trial and error and guidance) with an environmental set-up to assure optimal learning of motor skills. This may include special equipment to facilitate optimal motor learning. (see the Appendix for related pictures & videos) The following are areas to prioritize:

- Assess and identify sensory processing patterns to include assessing and identifying supports and barriers to basic daily activities- including sleep, feeding, toileting, etc. Rule out medical complications for any barriers or difficulties identified, and then develop supportive interventions for these areas. Activities: Sign Up EARLY (months to years before child ready as usually there are waiting lists) such as hippotherapy and aquatic therapy. (figs 26,27,28,29)
- Appropriate sensory inputs into your intervention. For example, proprioceptive and deep tactile input (input to joints- pushing, pulling, hugging, squeezing, jumping) can be calming, while vestibular input (swinging, rocking, head movements, bouncing) can have both calming and dysregulating affects that may support or hinder regulation. Walz & Baranek (2007)1 found high rates of sensory processing variability and dysfunction in children with Angelman syndrome.
- When needed for schools, The Peabody Developmental Motor Scales II (PDMSII) evaluation tool is composed of six subtests that measure interrelated abilities in early motor development. It is designed to assess gross and fine motor skills in children from birth through five years of age. When needed for insurance or schools, some people use PDMSII to capture videos and pictures of functional gains to show progress to parents. For more information check out this website:

Quotes from a few therapists who have worked with individuals with Angelman syndrome

"Being flexible to match the child's mood and willingness to participate while still reaching their goals is a fundamental of pediatric therapy."

"Being creative and being able to work on the fly."

*"Being persistent and patient, no, really P*E*R*S*I*S*T*E*N*T AND P*A*T*I*E*N*T...could be a month of dedicated time to allow the infant/child to own 1 skill."*

"Making all therapy functional so parents can tweak their support/hand placement and positioning for: p diaper changing."

FOCUS POINTS

MOTIVATION

- Depends on what captures your child's attention and what keeps their attention. In the case of some it could be their favorite things like magazines, musical toys, light up toys, build magnets, or specific people. Keep these toys "special" to use only during engaged parent play or therapist play, not during independent play time.

ENVIRONMENT

- Static (consistent) environment to master skill, then dynamic (same location with distractions added) environment, then novel (new location) static then novel dynamic (new location with distractions added).
- Limit flat play time to playpen, not open floor. This will allow child to get input seeking when rolled into sides of playpen. Fix toys/motivation from at the top on side out of reach or across the middle. It also encourages pushing up on hands to view and eventually pulling to stand, rather than rolling.
- When growing playpen space, make space with a "play-yard" a narrow rectangle to facilitate moving forward, not rolling sideways (fig.1). Focus on toy placement at nipple level (not eye level) to engage eyes in downward gaze to engage tummy muscles for back play, playpen, crib mobiles, car seats and, supported sitting.
- Obstacle Course: when leaving child for safe free play, set up environment so that child needs to problem solve to get their favorite toy drawer/closet/bin (rather than placing toy on lap) (fig.2).
- Limit toy selection to a choice of 2 held separately for focus playtime (fig.3).
- Increase body awareness by hiding favorite soft toys under shirt (start with front move to back, shorts leg then pant-leg) for free play time challenge (fig.4).
- Once up and walking, even with support, get all play up off the floor using supported tall kneeling (fig.5,6,7,8), dynamic standing support, or sitting in a chair reaching in a bucket on the floor.

STABILIZE

- Very early on, stabilize as much of the body as you can, including the neck, to get control of eye gaze. I have found being at the head of the infant, having an infant on back with a weighted blanket, engaging in face to face while infant locks upward eye gaze is a fun game for infants with parents and siblings.
- Restrict joints and provide an "external skeleton" (bracing as much as possible). Use elbow splints early to get weight bearing through hands in 4 point supported sitting and then supported quadruped (fig. 9,10).
- Start very early eliciting balance reactions(fig.11) in functional ways as well as getting the hand position as low on the trunk as possible, with the goal of all support at diaper level.
- A favorite: Hold the infant at the trunk, sit the infant on changing table facing you, rolling to the side, then to the back to change the diaper. Then rolling the infant to the side, to sitting facing you, then picking up from the changing table. (Focus on 3: "SIT SIDE BACK" then "BACK SIDE SIT" to slow yourself down.) Be sure to change head placement from one end of table to the other so that you engage both the left and right sides of the trunk. As the infant develops you are looking for hand to go out, as a side protective reaction.
- When moving to standing, use elbow splints (elbow& knee splints are interchangeable at this age) on knees to get weight bearing, as you hold child at waist from behind (fig.19).
- Then, start to remove one brace at a time, keeping bracing on the stronger side rather than weaker for neurological training. Then use support at the trunk moving down the legs with support as control improves, then to combine with variable input support, to allow a safe environment to explore and find midline.
- Using lit/musical toys to facilitate crossing midline (i.e., use of left hand to reach to right to grab toy) and reaching to get additional trunk rotation in various positions including lying down, sitting, kneeling and standing. Also provides weight shift stabilization needed for higher level activities.

SUPPORT

- Our hands show the child where support will come from: our tendency is to hold the child up. BUT focus rather on slightly pushing child's feet down into the surface, to allow them to gain a better understanding of where their support surface is coming from.
- Use support from behind the child with all activities such as tall kneeling and standing during dedicated engaged play as children will naturally get support from surfaces in front of them.

- Sitting infants in cross-leg sitting with support at ankles and with no other trunk support (fig.12).
- Inside corner support in standing (fig.13).
- Allow for variable non-human support, such as flexible rope draped at variable heights. The tighter the rope the more support and the looser the rope the more the child needs to react with trunk muscles to maintain upright (fig.14,15,16,17,18,19,20).
- When walking, get away from handheld as soon as possible and try using variable hand input to shoulder; try holding a firm toy while the child holds the other side progressing to floppy toy in the same manner.
- Walking in chest level in water, input at the pelvis in the beginning, possible weighted vests to keep legs down and feet on floor (fig.26).
- Walking on a treadmill with variable support including up to a Lite-Gait type support.
- Walking while carrying objects first in 1 hand and progressing to 2 hands, as able.

CORE (Ask therapist for more details to start core work early)

- Use of breathing facilitation to improve diaphragm function and core musculature to improve balance.
- Rib mobilizations and myofascial work to improve trunk mobility, breathing patterns,

EQUIPMENT

It is imperative to have set ups in the home to facilitate movement with proper balance of guidance and just the right challenge. Individuals with Angelman syndrome may take a longer period of repetitive positioning, movement and/or choice limitation to own the experience. The equipment suggestions may carry over into next area of development depending on the individual.

For Infants

All postures, appropriate toy selection with early isolation of toys to the choice of 2, early opportunities for emerging infant motor skills such as prone progression, rolling, sitting, kneeling and crawling. Aids for transitioning such as wedges, foam steps, proper table heights for pull to kneeling or standing etc.; may include such garments as a SPIO.

- **SPIO of varying support levels (figs.6,10,21)**
  The SPIO is ideal for children with poor core muscle activation, stabilization or weakness.
  Provides shoulder-trunk-hip stability and midline orientation and increases body awareness. Both tops and bottoms. www.spioworks.com

- **Bath Ring**
  Once sitting with support at trunk, the bath ring allows an individual to have more autonomy in the bath, while building trunk strength and control of freedoms of movement within the ring. It supports play and body stability training. See product example on Amazon.

- **Elbow Extension Splints (for elbows and/or knees) (figs.9,10,19)**
  An elbow or knee extension splint provides an extra set of hands while giving joint control to allow for isolated joint control work. Gives you an extra pair of hands to challenge individual with AS without hand support for continued body control development during workout sessions.
  See the BraceAbility Elbow Immobilizer on Amazon

- **Weighted Blankets/Vests (figs.23,24)**
  Helps to control bodies by providing firm pressure. Individuals are provided with increased sensory feedback to help with body control and awareness. Please check with therapist about appropriate weight of blanket for your individual. www.lunablanket.com/products/luna-weighted-blanket

For Toddlers

Emerging walking with necessary supports but adequate challenge to reach independence (walkers as needed, orthoses), swimming and climbing, early fine motor skills. Repeating simple phrases such as, “Give me” when taking an object and continuing daily through elementary.

- **Wall mounted toys**
  Allow for motivation for pushing vs. pulling training

- **Crawling Aid**
  Very helpful to keep children of any age moving independently on hands and knees if walking is not yet attained. See FLAGHOUSE Adjustable Crawler on Amazon

- **Spiral Orthoses (Show the attached images to your orthotist and physical therapist.)**
  Can provide just the right amount of stability and support to engage the individual's larger muscle/motor control. Can help by giving intermittent input into legs and improving walking abilities. Orthotist and PT’s may not recommend this type of support, but for individuals with Angelman syndrome, spiral orthoses are game changers. Individuals with Angelman syndrome have the strength, so they don’t need fixed support, but they do need the support to learn where midline is, and the spiral orthoses gives this variable input.

- **BILLY Shoes**
  Orthopedic footwear for individuals with ankle foot orthosis (AFO).
  billyfootwear.com

- **Safety**
  o Enclosed Beds: Safety Sleeper by Abram’s Nation
  o For Travel: Safe Place Bedding
  o Dutch Door (1/2 door) (fig.25): See product at Home Depot

For Elementary

Addressing higher motor skills- adaptive bike, running and engagement in group motor activities, especially for the school-aged child who will be in class and working with school staff to make choices, etc.

Bikes

- Adaptive Bikes: designed specifically to the individual. The bikes are designed for mobility, therapy, recreation, and fun!
  - o Rifton
  - o Freedom Concepts
  - o Worksman

- **Ride-Alongs / Trailers**
  Weehoo

- **Safety Helmet (fig.22)**
  - o If walking balance and independence are at odds a safety helmet can aid in progress.

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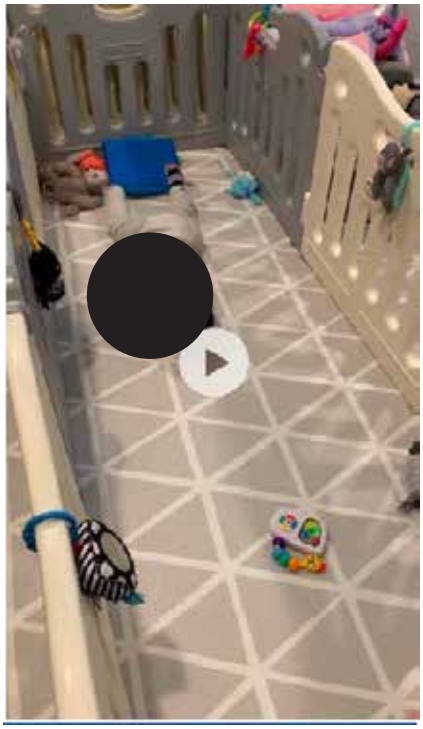
   https://www.orpha.net/data/patho/Pro/en/AngelmanGuidelines2011.pdf

APPENDIX OF PICTURES & VIDEOS



FREE TIME PLAY:
Play-yard rectangle: to encourage movement forward place toys out of reach.

Obstacle Course: when leaving child for safe free play, set up environment so that child needs to problem solve to get to favorite toy draw/closet/bin.

Limit Choice of toys during focused playtime.

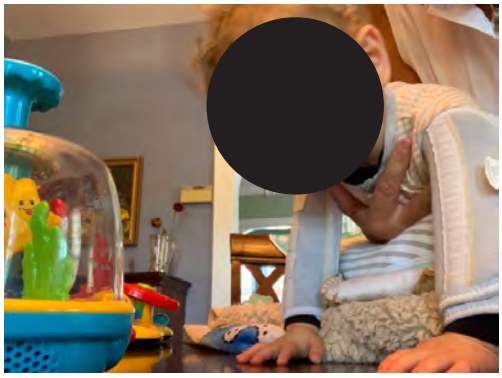
Hide soft toys under clothes: start front of shirt, move to back of shirt, shorts leg, then pant legs.

PLAY POSITIONS

Kneeling at Slant Toy

Kneeling with Trunk Rotation (SPIO on with Extra Back Support)

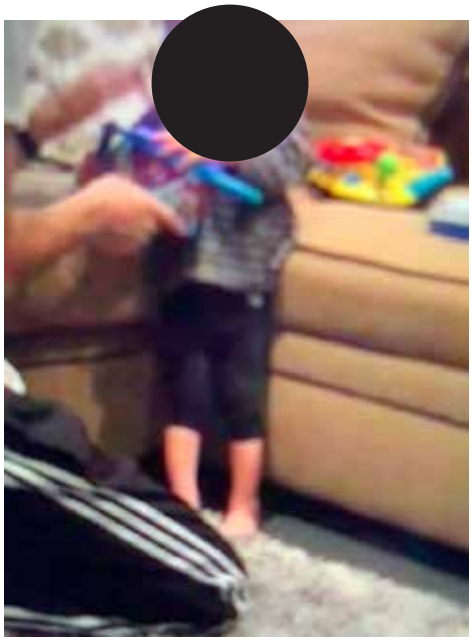
Tall Kneeling with Posterior Support



All Fours with Elbow Braces

One Protective Reaction:
right hand out to side

Crossed legs sitting with
Support at Ankles

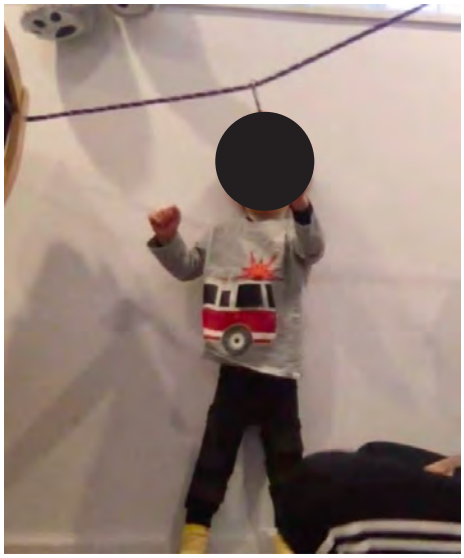


Posterior support standing
on inside corner

Rope draped at adjustable heights for dynamic support play: Walking or Static Standing

Dynamic Support of Bolster & Rope

Tall kneeling with Rope



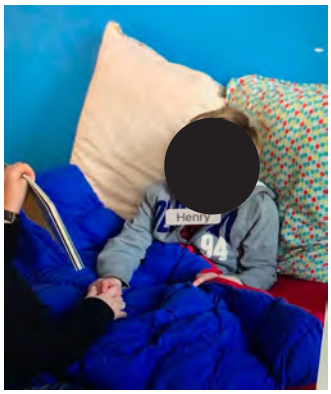
Rope with wall support. Knee Brace on Stronger Leg Only.

Home Made Dynamic Surface Support of Light Saber & Swiffer ;)

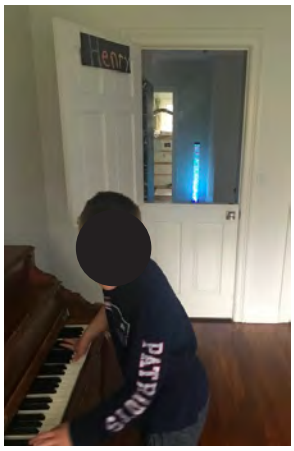
EQUIPMENT

Full SPIO suit on:

Helmet for increased safety with walking

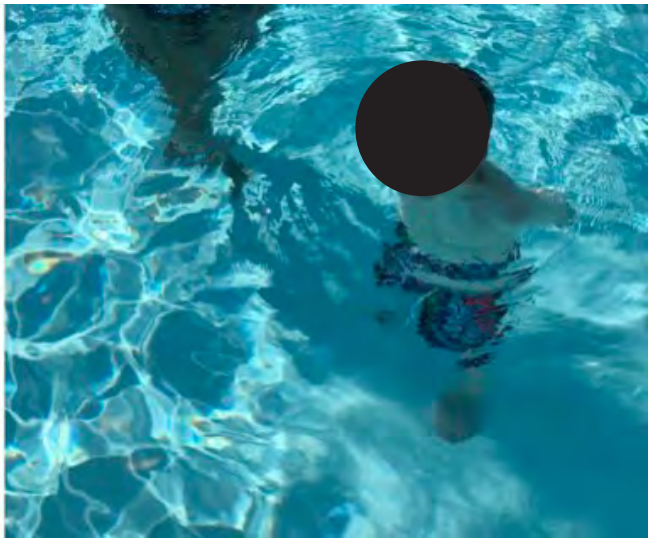


Weighted Blankets of Various Sizes



Dutch(1/2) Door

EXTRA FUN ACTIVITIES:
Sign Up EARLY (months to years before child ready as usually there are waiting lists)



Walking in shoulder high water: may use weighted vest or weights at waist to keep feet on ground.

Hippo-therapy and/or Therapeutic Riding

Skiing feeling the wind in my face

Buddy Surfing

LADDER
Learning Network
For Patients. For Providers. Together, Toward The Cure.
A Partnership Of

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Part of the Ladder Learning Network

Share Your Feedback About Today's Visit

Your feedback helps ASF Clinics provide the best possible care for individuals with AS.

Take The Online Clinic Survey
Angelman.org/Survey

Stay Connected with Angelman Syndrome Foundation

Add yourself to our email list and stay informed about how ASF can help you on your journey.

Complete the ASF Contact Registry
Angelman.org/ContactRegistry

Enroll in LADDER

Now that you have visited an ASF Clinic, enroll your individual in the LADDER Database. It connects information from research studies and clinic visits to create a higher level of understanding of AS.

Learn More About LADDER And Enroll
Angelman.org/Ladder

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The mission of the Angelman Syndrome Foundation is to advance the awareness and treatment of Angelman syndrome through education and information, research, and support for individuals with Angelman syndrome, their families and other concerned parties. We exist to give all of them a reason to smile, with the ultimate goal of finding a cure.

Info@Angelman.org | 1-800-432-6435 | 3015 E. New York St. Suite A2 #285, Aurora, IL 60504

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