Symposium Title: Advances in Characterizing Developmental Trajectories in Angelman Syndrome across the Lifespan

Chair: Anjali Sadhwani, Ph.D.¹ & Katherine C. Okoniewski, Ph.D.²

Discussant: Terry Jo Bichell, MPH, Ph.D.³

Overview: Angelman syndrome (AS) is a rare neurogenetic syndrome (1 in 15,000) that is characterized by severe intellectual disability with substantial impairments in cognitive, language, and motor functioning, minimal or absent speech, seizures, and ataxia. Many affected individuals also exhibit complex medical and psychiatric features that impact quality of life. AS is caused by lack of expression of the maternally-inherited UBE3A on chromosome 15q11q13 due to one of four etiologies: deletion of the critical region of the maternally-inherited chromosome 15 that encompasses UBE3A, paternal uniparental disomy (UPD) for chromosome 15q11q13, imprinting defects that alter expression of the maternally-inherited copy of UBE3A, or a pathogenic variant in the maternally-inherited UBE3A (Clayton-Smith & Laan, 2003). Approximately 70-75% of individuals with AS have a deletion, 8-9% have UPD, 7-8% have imprinting defects, and 11% have UBE3A mutations. Although a number of studies have quantified the medical profiles of individuals with AS, far fewer have characterized the neurodevelopmental and psychiatric features, limiting translational efforts to provide effective supports for individuals with AS and their families. This gap is due, in part, to the challenges of accurately quantifying neurodevelopmental and psychiatric features in children with AS who (1) may not be able to participate in traditional assessment tasks that rely heavily on motor and language skills and (2) are geographically dispersed, limiting opportunities for large-scale clinical research. In this symposium, four early career psychologists will discuss their recent efforts to more accurately quantify the AS phenotype across the lifespan, using both traditional and novel assessment methods. First, Dr. Anjali Sadhwani will describe emerging data from the Angleman Natural History Study, a comprehensive, large-scale examination of cognitive, motor, language, and adaptive behavior skills across the lifespan. Next, Dr. Casey Okoniewski will describe anxiety and separation distress in AS using a novel parent-report measure specifically tailored for individuals with AS. Third, Wei Siong Neo will describe early challenging problem profiles in young children with AS, as well as current efforts to leverage both psychometric analyses and parent input to improve measurement of these features in young children. Finally, Lisa Hamrick will describe novel methods for quantifying prelingual vocalizations in children with neurogenetic syndromes and limited speech, including children with AS. Together, these papers will showcase both the challenges of characterizing neurodevelopmental phenotypes in individuals with AS, as well as a number of creative solutions for improving understanding of the AS phenotype. Finally, discussant Dr. Terry Jo Bichell – a parent of a child with AS, advocate within the AS community, and researcher – will discuss these findings in the context of broader community efforts to advance understanding of AS and related treatments to optimize outcomes for affected individuals and their families.

Paper 1 of 4

Paper Title: A Longitudinal Investigation of Developmental and Adaptive Functioning In Individuals with Angelman Syndrome

Authors: Anjali Sadhwani¹, Anne Wheeler², Lynne M. Bird³, Carla Bann⁴, Rene L. Barbieri-Welge⁴, Lucia T. Horowitz⁵, Lisa M. Noll⁶, Sarika Peters⁷, Rachel J. Hundley⁷ & Wen-Hann Tan¹

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Introduction: Angelman syndrome (AS) is a rare neurodevelopmental disorder with a prevalence of 1 in 15,000 (Buckley, Dinno, & Weber, 1998; Clayton-Smith & Laan, 2003; Kyllerman, 1995). Individuals with AS have global developmental delay, severe intellectual disability, and minimal or absent speech (Clayton-Smith & Laan, 2003). Although AS is a neurodevelopmental disorder that was described over 50 years ago, characterization of the developmental trajectory over time has been limited (Peters et al, 2004; Gentile et al, 2010). The AS Natural History Study initiated in 2006 is a longitudinal study in which each participant is evaluated at a study site at regular, typically annual, intervals. The purpose of this presentation is to provide detailed characterization of the cognitive, language, motor and adaptive functioning of individuals with different subtypes of AS and delineate how it changes over time.

Method: At each study visit, participants underwent a comprehensive neurodevelopmental evaluation. Developmental functioning was assessed by a psychologist using either the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) (Bayley, 2005b) or for participants who exceeded performance thresholds on the Bayley-III, the Mullen Scales of Early Learning (MSEL) (Mullen, 1995). In addition, caregivers were interviewed about the participants’ adaptive functioning using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II).

Results: The AS Natural History study enrolled 302 individuals with a cytogenetic or molecular confirmation of AS (age range: 5 months to 40½ years old). Approximately 72% had a deletion, 11% had a UBE3A mutation, and the remaining 17% had UPD, imprinting defect, or abnormal methylation not further classified. Mean age at the first visit was 6.0 years. Approximately 95% of the participants were less than 20 years at age of first visit. About 24% of the cohort had only one visit. Longitudinal analyses for the entire dataset is ongoing and will be reported in detail. Preliminary results indicate that across genotypes, expressive language skills, written language skills and community skills were low and did not increase over time. For the remaining domains of functioning, there were significant subtype differences; participants who had a deletion in the chromosome 15 AS critical region had slower rate of growth compared to those with UPD/imprinting defects or UBE3A mutations. Additional subtype analyses will be discussed including controlling for sex and seizures.

Discussion: To our knowledge, this is the first study to characterize the developmental and adaptive functioning of individuals with AS over time. Results indicated that the developmental profiles of individuals with AS vary with subtype. Limitations of the study, implications and directions for future research will be discussed.

References/Citations:


Paper 2 of 4

Paper Title: Anxiety and Separation Distress in Individuals with Angelman Syndrome

Authors: Katherine C. Okoniewski8, Amanda Wylie2, Danielle Toth2, Margaret DeRamus5, Laura Hiruma8, Anne Wheeler2,8

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**Introduction:** Angelman syndrome (AS) affects approximately 1 in 10,000 to 12,000 individuals and is caused by reduced expression of the **UBE3A** gene found on the maternally-inherited chromosome 15 at q11-q13 (Kyllerman, 1995). The **UBE3A** gene is associated with synaptic development and neural plasticity, and its reduced expression in AS is associated with severe cognitive and motor impairments and limited or absent speech (Thibert, Larson, Hsieh, Raby & Thiele, 2013). Furthermore, prevalence rates of ASD in AS range from 34-81% (Richards, Jones, Groves, Moss & Oliver, 2015), potentially reflecting the challenge of differentiating ASD-specific behaviors in AS from behaviors related to the severe developmental delays often present in this population. Similarly, anxiety-like symptomology has been captured clinically via parent report, with little research having explored the anxiety-like profile in these individuals, or differentiation between this behavioral profile and one commonly seen in those with severe developmental delays.

**Method:** Participants included parents or primary caregivers of 99 individuals with AS. Approximately 53% of participants were recruited from a specialized AS clinic, with the remaining having completed questionnaires during an Angelman Syndrome Foundation Family Conference (47%). All participants completed targeted questionnaires to explore behavioral profiles including select questions from the Anxiety, Depression, and Mood Scale (ADAMS). For those who attended the clinic, additional information regarding the individual with AS’s developmental age, functional skills, communication level, and other behavioral concerns was collected via direct assessment and caregiver interview. The individuals with AS ranged in age from 10 months to 36 years (Mean = 12.2; SD = 10.1). Sex distribution was equal.

**Results:** Almost all individuals with AS were reported to have at least 1 symptom of anxiety or increased agitation and 43% were reported to have 10 or more symptoms. Being clingy, not being able to relax, trembling and displaying nervous habits were the most commonly endorsed symptoms with over a third being reported to have a moderate to severe problem with these symptoms. Over half of the participants were reported to have a preferred caregiver and of those, the majority (65-73%) demonstrate agitation when separated from that preferred caregiver. Individuals with the **UBE3A** mutation subtype were more likely to be rated as having higher anxiety than the other subtypes of AS. Other challenging behaviors were the strongest predictor of parent-reported anxiety.

**Discussion:** This is one of the first studies to empirically document the severity and frequency of anxiety symptoms, including separation distress in individuals with AS. Considerations with regard to measurement issues, as well as clinician derived, consensus-based interventions to support families in helping reduce anxiety for this population will be discussed.

**References/Citations:**

**Paper Title:** Characterizing and Improving the Measurement of Early Challenging Behaviors in Angelman Syndrome

**Authors:** Wei Siong Neo⁹ & Bridgette L. Tonnsen⁹

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Introduction: Angelman syndrome (AS) is a rare neurogenetic syndrome (NGS) characterized by severe cognitive impairment, jerky movements, minimal use of speech, happy demeanor, and interest in social interactions (Williams, 2010). Similar to other NGS, individuals with AS often experience comorbid challenging behaviors and psychopathology, including aggressive and self-injurious behaviors (Larson et al., 2015), autism features (Bonati et al., 2007), hyperactivity (Clarke & Marston, 2000), and sleep disturbances (Abel & Tonnsen, 2017). However, limited research has examined the emergence of these challenging behaviors in toddlers and preschoolers with AS, and cross-syndrome comparisons have also received relatively little attention. This paper aimed to characterize parent-reported early childhood challenging behavior profiles in AS and improve the measurement of these early precursors of psychopathology by leveraging both psychometric analyses and parent inputs.

Method: Data from three interrelated studies on challenging behaviors in young children with AS were integrated. First, we described early childhood challenging behavior profiles in 30 infants and toddlers with AS using the Child Behavior Checklist for Ages 1½-5 (CBCL; Achenbach & Rescorla, 2000), as well as contrasted their profiles with children of other NGS and those without developmental concerns. Next, we described psychometric efforts, such as confirmatory factor analyses and item-level techniques, to validate the CBCL in a cross-syndrome sample of young children with NGS (n = 117) that included AS. Finally, we described qualitative results from a national parent survey that solicited suggestions for improving psychological assessments for children with AS and other NGS.

Results: Infants and toddlers with AS had atypically elevated scores for challenging behaviors related to somatic complaints ($z = 3.40, p < .01, r_{pb} = .40$), withdrawn tendencies ($z = 6.61, p < .001, r_{pb} = .77$), and attention ($z = 4.89, p < .001, r_{pb} = .57$). In addition, cross-syndrome comparisons with Prader-Willi and Williams syndromes indicated greater withdrawn tendencies and autism spectrum problems in AS ($z > 2.81, ps < .01, r_{ps} > .39$). Psychometric analyses revealed that internal consistency of most narrowband and DSM-oriented CBCL scales was acceptable (as > .70) and similar to publisher-derived norms. However, unidimensionality of these scales, as applied to populations with NGS, varied considerably according to standard model fit indices; most of the narrowband CBCL scales attained a good fit (RMSEAs < .057; CFI$s > 0.953; TLI$s > 0.964$) whereas most of the DSM-oriented CBCL scales required item-level modifications to enhance fit (RMSEAs > .073; CFI$s < 0.931; TLI$s < 0.912$). Omitted items to improve model fit (e.g., item “repeatedly rocks head or body” on the scale of autism spectrum problems) were broadly corroborated by qualitative parental suggestions on improving psychological assessments for children with AS and other NGS, such as central themes of greater consideration of comorbidities in these children and adoption of syndrome-specific scoring mechanisms.

Discussion: Differential patterns of early challenging behaviors were observed across NGS, with early emergence of such behaviors in AS, highlighting the importance of cross-syndrome characterization efforts to understand commonalities and distinctions in atypical developmental trajectories in AS and other NGS. The measurement of challenging behaviors in young children with AS and other NGS can be enhanced with theoretical advancements in psychometric approaches as well as stronger integration of parent-informed models. Our study provides initial but promising evidence on the value of syndrome-specific and family-centered understanding of early challenging behaviors, which will lay the foundation for targeted interventions to optimize developmental outcomes for children with AS and other NGS.

References/Citations:


**Paper Title:** Measurement and Characterization of Early Social Communication in Children with Angelman Syndrome

**Authors:** Lisa R. Hamrick⁹, Bridgette L. Tonnsen⁹

**Introduction:** Individuals with AS experience severe language and communication deficits, with most individuals never mastering the functional use of more than one or two single words (Clayton-Smith & Laan, 2003). However, our understanding of early developmental processes or mechanisms by which these deficits occur is limited, in part due to the lack of appropriate measures that have been validated for assessing early social communication skills in AS. In this presentation, I will describe current efforts to address this issue through an ongoing longitudinal study of early development in neurogenetic syndrome populations. First, I will present findings from two studies using different approaches to characterize early social communication skills in AS by validating a popular parent-report social communication screening measure. Next, I will present a novel approach for measuring spectral features of early vocalizations that have demonstrated associations with language and autism outcomes in other neurogenetic groups and which can be extended for use in AS.

**Methods:** Participants are 38 participants with AS who are participating in an ongoing longitudinal study of early development in neurogenetic syndrome populations. Mothers of children with AS complete online surveys about their child’s development every 6 to 12 months. Between 1 to 4 observations have been collected for each participant for a total of 86 observations across participants, with ages ranging from 6 to 71 months. At each survey, mothers complete the Communication and Symbolic Behavior Scales – Infants-Toddler Checklist (CSBS-ITC; Wetherby & Prizant, 2003), a 24-item screening measure used to assess for early social communication delays across 3 composites: Social, Speech, and Symbolic. Our first study reports broad profiles and within-person growth in a subset of the overall sample (n=15) who had completed at least 2 observations of the CSBS-ITC. Our second study uses all available CSBS-ITC data to analyze the sources of measurement variance and reliability for this measure using generalizability theory. Our final study will describe both automated and spectral features of early vocalizations in AS, collected using a specialized audio recorder (Language ENvironment Analysis System, or LENA; Xu, Yapanel, & Gray, 2009) that captures a day-long recording of the child’s vocalizations and language environment (data collection in beginning stages, projected sample n=10). These procedures and analyses will build on recent work examining these features in 9-month-olds with fragile X syndrome.

**Results:** In our first study, we found that normative scores on the CSBS-ITC captured minimal variability in social communication skills among individuals with AS, with 88% of participants receiving standard scores at the measure floor, and 100% of participants scoring in the range of concern. However, rates of floor effects for CSBS-ITC raw scores were much lower, with only 24% of participants scoring at the measure floor in the Speech composite. Nevertheless, raw scores did not demonstrate significant associations with age and did not reflect meaningful growth in skills over a 6-month interval in AS. In our second study, we found that the majority of variance (47.57%) in CSBS-ITC raw scores among individuals with AS was explained by item-level content. In contrast, the child’s age only explained 1.16% of the variance in scores, again suggesting that the social communication skills being measured by CSBS-ITC raw scores are not changing systematically with age in AS. Our final study will examine novel approaches for circumventing the limitations of existing informant-based social communication measures by analyzing day-long naturalistic vocalization samples. We will use these samples to describe several central features of the language environment, including the number of sounds the child makes, how many adult words the child is hearing and how
many back-and-forth exchanges the child has, as well as developmental and spectral features of early vocalizations, such as volubility, vocal maturity, vocalization pitch and vocalization duration. We will focus specifically on how we have leveraged both commercially-available equipment and supplemental processing pipelines to generate these data, including challenges and benefits of each approach. We will also present preliminary data from children with AS, with the hypothesis that similar to our recent work in fragile X syndrome (Hamrick, Seidl, & Tonnsen, in prep), canonical complexity and volubility will relate to language outcomes at 24 months, whereas average pitch will relate to later autism outcomes.

Discussion: Efforts to validate an existing tool for measuring early social communication in AS have demonstrated that the CSBS-ITC may capture some variability in skills among individuals with AS, but that it is not sensitive enough to capture meaningful change over time. Measures of spectral features of early vocalizations have shown promise in predicting later language and autism outcomes in another neurogenetic syndrome population; thus, these methods may fill the need for measures of early social communication that can detect nuanced, meaningful change in AS. Importantly, by identifying appropriate tools for measuring early social communication in AS, we can begin to understand the mechanisms and pathways underlying these deficits, leading to improved treatment approaches for this population.

References/Citations: