

### **Behavioral and Developmental Issues**

### Hyperactivity

Hyperactivity is a very common behavior in AS and it is best described as hypermotoric. Essentially all young AS children have some component of this increased motor activity and males and females appear equally affected. Infants and toddlers may have seemingly ceaseless activity, constantly keeping their hands or toys in their mouth, moving from object to object. In extreme cases, the constant movement can cause accidental bruises and abrasions. Grabbing, pinching and biting in older children have also been noted and may be heightened by the hypermotoric activity. Persistent and consistent behavior modification helps decrease or eliminates these unwanted behaviors.

In infants, the attention span can be short and social interaction is hindered because the AS child cannot seemingly attend to facial and other social cues. In childhood however attention abilities may increase, often associated with apparent curiosity as well. Attentiveness may then become sufficient to begin teaching sign-gesture language and other communication techniques. Observations in young adults suggest that the hypermotoric state decreases with age. Most AS children do not receive drug therapy for hyperactivity although some may benefit from use of such medications. Use of calming or sedating medications like Risperidone (Risperdal) is not generally advised but may be useful in rare cases. There is a tendency toward weight gain (with the use of certain neuroleptics), and these drugs are also associated with more side effects. Thus far, there are no formal clinical trials examining the efficacy of stimulant medications or neuroleptics to treat hyperactivity/impulsivity in AS.

#### Laughter and happiness

It is not known why laughter is so frequent in AS. More recently, advances in neuroimaging have assisted researchers in uncovering the cortical and subcortical regions of the brain that are associated with laughter 16 in normal individuals. Specifically, the results of these studies indicate that the humor-processing pathway includes parts of the frontal lobe brain area, important for cognitive processing; the supplementary motor area, important for movement; and the nucleus accumbens, associated with pleasure. The supplementary motor area is most involved in the motor aspects of humor (laughing and smiling). Recent neuroimaging studies show that increased activation in the supplementary motor area is correlated with laughter, as is activation in the dorsal anterior cingulate area. Both of these regions receive rich dopamine input from the ventral striatum. A recent functional imaging study also showed that the cortical structures involved with humor and laughter include: the temporo-occipital junction, inferior frontal gyrus/temporal pole, and the supplementary motor area/dorsal anterior cingulate, all in the left hemisphere. The same study also implicated that several subcortical structures, including the amygdala, ventral striatum/nucleus accumbens, ventral tegmental area, thalamus, and hypothalamus are also

involved in humor and laughter. Taken together, the results suggest that the left hemisphere plays a distinct role in the humor processing pathway, and subcortical, dopaminergic structures play an important role in humor and laughter.

Studies of the brain in AS, using MRI or CT scans, have not shown any defect suggesting a site for a laughter-inducing abnormality. Recent neuroimaging studies in deletion positive patients with AS d reveal some abnormalities within the humor processing pathway. Specifically, individuals with AS exhibit reduced volume in the nucleus accumbens as well as the globus pallidus within the left hemisphere, and these regions are associated with both the reward mechanisms associated with humor/laughter as well as the motor aspects of laughter. The results of diffusion tensor imaging studies also reveal abnormalities (reduced fiber density and coherence) within white matter pathways in the limbic system in patients with AS, as well as prefrontal regions, and differences in the fibers projecting to and from the internal capsule that may account for difficulties with the regulation of laughter. The results of magnetization transfer imaging studies reveal differences in the thalamus (fibers projecting to/from the thalamus) that could also account for some of these difficulties. Although there is a type of seizure associated with laughter, termed gelastic epilepsy, this is not what occurs in AS. The laughter in AS seems mostly to be an expressive motor event; most reactions to stimuli, physical or mental, are accompanied by laughter or laughter-like facial grimacing. Although AS children experience a variety of emotions, apparent happiness predominates.

The first evidence of this distinctive behavior may be the onset of early or persistent social smiling at the age of 1-3 months. Giggling, chortling and constant smiling soon develop and appear to represent normal reflexive laughter but cooing and babbling are delayed or reduced. Later, several types of facial or behavioral expressions characterize the infant's personality. A few have pronounced laughing that is truly paroxysmal or contagious and "bursts of laughter" occurred in 70% in one study. More often, happy grimacing and a happy disposition are the predominant behaviors. In rare cases, the apparent happy disposition is fleeting as irritability and hyperactivity are the prevailing personality traits; crying, shrieking, screaming or short guttural sounds may then be the predominant behaviors.

### **Mental Deficiency and Developmental Testing**

Developmental testing is compromised in AS individuals due to attention deficits, hyperactivity and lack of speech and motor control. In such situations, test results are invariably in the severe to profound range of functional impairment. It is possible however that the cognitive abilities in AS are higher than indicated from developmental testing. Nevertheless the developmental delay is still consistently in the functionally severe range and formal psychometric testing seem to indicate a ceiling for developmental achievement at around the 24-30 month range. In general, Angelman syndrome individuals have relative strengths in nonverbal reasoning skills and with social interactions that are based on non-verbal events.



As we learn more about the different genetic classes of AS it appears that patients with the common chromosome deletion type of AS have relatively more severe developmental impairment. Older individuals with AS have been evaluated in terms of their adaptive functioning and the table, adapted from Summers and Pittman, lists some aspects of these studies.

Studies of Adaptive Functioning in AS	Study and Details Findings
Smith et al., 1996 Ages 334 years, all had deletions	Teenager and adults were all dependent on assistance with feeding, toileting and dressing
Moncla et al., 1999 Ages 15-36 years; compared deletion to non-deletion cases	Vast majority with deletions were dependent on assistance for feeding, toileting and dressing; majority of non-deletion cases did not need assistance for dressing and feeding
ClaytonSmith, 2001 Adults 2053 years; not in institutions and 82% had deletions	<ul> <li>85% could perform a simple task such as holding a utensil</li> <li>50% helped to undress themselves</li> <li>57% remained dry during the day (clock - trained) 11% overnight</li> </ul>
Sandanam et al, 1997 [40] Adult 2436 years, all in institutions and all had deletions	All were dependent for activities of daily living

Many young adults with AS learn to respond to personal cues and interactions. Because of their interest in people, they express a broad repertoire of feelings and sentiments and form close bonds/attachments to others. Individuals with AS participate in group activities, household chores and in the activities and responsibilities of daily living. Like others, they enjoy most recreational activities such as TV/movies, listening to music, physical activity, going to the beach, etc. There is a wide range, however, in the developmental outcome so that not all individuals with AS attain the above noted skills. A few will be more impaired in terms of their mental retardation and lack of attention, and this seems especially the case in those with difficult to control seizures or those with extremely pronounced ataxia and movement problems.

Fortunately, most children with AS do not have these severe problems, but even for the less impaired child, inattentiveness and hyperactivity during early childhood often give the impression that profound functional impairment is the only outcome possible. However, with a secure home and consistent behavioral intervention and stimulation, the AS child begins to overcome these problems and developmental progress occurs.



### **Autism and Related Traits**

Some of the associated clinical features of AS (e.g. hand-flapping, stereotypic behaviors, deficits in expressive language), overlap with certain features of autism. Generally speaking, clinicians should exercise caution when examining symptoms of autism within AS, because some AS patients have been mistakenly identified as having autism in lieu of AS, and some patients who exhibit features of autism when they are younger, may no longer exhibit these features as their cognition and their language skills improve. There are, however, some studies that specifically examine the frequency and magnitude of autistic traits in individuals with AS. While some researchers demonstrate a lack of autistic traits or very low incidence of autism in individuals with AS, several other studies have demonstrated that a percentage of individuals with AS do also meet criteria for autism. Individuals with AS and co-morbid autism are more likely to show decreased eye gaze, fewer social overtures, use fewer nonverbal gestures, use another person's body as a "tool" to communicate "for" them, have decreased shared enjoyment in interactions, and fewer socially directed vocalizations. In considering the differences in findings and clinical opinions across these studies, it is important to note that differences in sample selection, including differences in autism symptom severity across molecular subtypes of AS play a major role. Specifically, recent studies demonstrate that it is primarily deletion positive individuals with AS that exhibit greater symptom severity associated with autism, and within the deletion positive group, primarily children with larger, Class 1 deletions. Most recent findings indicate that these differences in symptoms of autism between the deletion subgroups are not related to differences in cognition (i.e. children with greater symptom severity were not necessarily lower functioning).

To summarize, studies seem to indicate that severity of autism symptoms in AS only affects a small proportion of AS patients, is associated with deletion size, and with a more aloof/withdrawn behavioral phenotype. There are four genes (NIPA 1, NIPA 2, CYFIP1, & GCP5) missing in Class I and present in Class II deletions (refer to diagram in Genetic Mechanisms that Cause AS section), one or more of which may have a role in the development of socialization skills and symptoms related to autism. For the small percentage of patients with AS who do exhibit more features of co-morbid autism, specific therapies such as applied behavioral analysis are quite helpful.

Repetitive behaviors (e.g. using objects or toys inappropriately), sensory interests (licking/mouthing, sniffing objects), and stereotypic motor movements (rocking, hand-flapping) are common to all individuals with AS and do not differentiate between those individuals who also have co-morbid autism. In fact, some individuals with AS do exhibit some compulsions, rituals (e.g. hoarding, hiding of food or objects, food fads), and repetitive interests/playing with unusual objects. These behaviors are primarily noted in older, and/or higher functioning individuals with AS and do seem to overlap with behaviors associated with Prader-Willi Syndrome; but the degree to which these associated behaviors are prevalent across the different molecular subclasses of individuals with AS has not yet been



investigated. Additionally, the degree to which these behaviors may be responsive to pharmacological treatment has also not been investigated in formal clinical trials.

#### Speech and Language

Some AS children seem to have enough comprehension to be able to speak, but in even the highest functioning, conversational speech does not develop. Clayton-Smith reported that a few individuals spoke 1-3 words, and in a survey of 47 individuals, Buntinx et al. reported that 39% spoke up to 4 words, but it was not noted if these words were used meaningfully. Children with AS caused by uniparental disomy may have higher verbal and cognitive skills; at times use of 10-20 words may occur, although pronunciation may be awkward. Finally, it is now clear that some AS individuals with a mosaic imprinting defect can have use of many words (up to 50 or 60) and a few of them can speak in simple sentences.

The speech disorder in AS has a somewhat typical evolution. Babies and young infants cry less often and have decreased cooing and babbling. A single apparent word, such as ""mama,"" may develop around 10 - 18 months but it is used infrequently and indiscriminately without symbolic meaning. By 2-3 years of age, it is clear that speech is delayed but it may not be evident how little the AS child is verbally communicating; crying and other vocal outbursts may also be reduced. By 3 years of age, higher functioning children with AS are initiating some type of non-verbal language and use nonverbal gestures as a way in which to compensate for their expressive language deficits. Some point to body parts and indicate some of their needs by use of simple gestures, but they are much better at following and understanding commands.

Others, especially those with severe seizures or extreme hyperactivity, cannot be attentive enough to achieve the first stages of communication, such as establishing sustained eye contact. The nonverbal language skills of AS children vary greatly, with the most advanced children able to learn some sign language and to use such aids as picture - based communication boards. Please refer to the section in this document on Communication for more details about the language and communications abilities, and the therapy approaches, for those with AS.

#### Communication

All children with AS communicate, some more effectively than others. Communicative attempts occur frequently in conjunction with individuals' overall desires to socially interact with others, an area of relative strength. When they are unable to communicate effectively, children may resort to problem behaviors such as pulling hair, pushing, hitting and biting to express their wants, needs, and feelings. It is important to recognize the vast majority of these behaviors are communicative attempts that occur when individuals lack access to other more conventional and socially appropriate methods of expressing themselves. We Source: 7th edition Facts about Angelman Syndrome by Charles A. Williams, M.D., Sarika U. Peters, Ph.D., Stephen N. Calculator, Ph.D. in 2009



can expect to see these behaviors fade once individuals learn alternative means of conveying the same intents, such as gestures and other forms of Augmentative and Alternative Communication (AAC). Children have no further need to scream if activating a message on a communication device results in the same desired outcome (e.g. gaining a teacher's attention) more efficiently and with less effort. Behavior problems more often reflect others' inabilities to provide children with effective and appropriate methods of communication than intrinsic limitations of the children. Still all individuals with AS demonstrate communication difficulties to some extent. Problems in this area have implications for most aspects of education and daily living and should thus be a focal point in all instructional programs. Communication skills are critical in order for children to access the general education and special education curriculums and participate actively throughout the day. Whether we are referring to physical education, reading, writing (e.g. with line drawings), art, music, lunch, or science, all of these events have corresponding communication demands that must be met for students to be full participants. It is thus essential that speech-language pathologists (SLPs) are available to other educators to problem solve communication strategies needed for children to be included throughout the day.

Communication challenges are especially evident in individuals with large deletions of the 15<sup>th</sup> chromosome. Those whose problems are linked to other genetic mechanisms, such as uniparental disomy and imprinting defects, typically exhibit stronger communication skills, both expressively and receptively, and more favorable prognoses for communication and language development. Irrespective of the underlying genetic mechanism, children with Angelman Syndrome are often unable to acquire and use speech as a primary method of communication. However, interventions including efforts to improve speech may be appropriate in some cases, particularly for individuals exhibiting genetic mechanisms other than large deletions, as some of these children may acquire a modest inventory of words and even phrases. Oral motor programs with other populations have yielded marginal results in terms of generalization to improvements in speech. There are no current studies documenting the efficacy of oral motor training for children with AS.

Given their poor prognoses for speech, individuals with AS need other means of expressing themselves. AAC systems may include unaided (e.g. gestures and signs) and aided (e.g. communication boards and various speech generating devices [SGDs]) methods that together constitute a multimodal system of communication. No one AAC system is appropriate for all individuals with AS and systems that are ideal for one individual may be of limited use to others.

Children with Angelman Syndrome usually self-select gestures as their preferred method of communication. Most of these behaviors, particularly early in their development, consist of 'contact gestures' which are dependent on physical contact with people and objects in order to be conveyed. Examples include pulling a parent by the hand toward a desired item that is out of reach or pushing away a non-preferred object offered to them. Distal gestures appear later and represent more abstract means of communication. These include extending their



hands and arms to indicate a desire to be picked up and pointing toward a desired object that is out of reach. The vast majority of individuals with AS have an inventory of natural gestures they are able to use functionally, especially when interacting with familiar people. These natural gestures can be modified to express a greater range of meanings more clearly and effectively using a system of Enhanced Natural Gestures, or, ENGs.

In light of their natural propensity to use gestures, communication interventions often rely on teaching individuals to use sign language. While they may indeed acquire anywhere from a few to more than a hundred signs, based heavily on the underlying genetic mechanism, individuals' motor problems often cause them to modify and distort targeted signs. This poses difficulty for others, particularly unfamiliar listeners, to understand. Listeners who are knowledgeable about sign language but not the versions of signs produced by some individuals may also encounter difficulty when interacting with these individuals. For this reason enhanced natural gestures (ENGs), which are by definition understandable to familiar as well as unfamiliar listeners, are often a preferred method of communication. Most individuals with AS supplement their gestures/signs with one or more types of aided communication. They may use systems of tremendously varying complexity, ranging from touching a preferred object to make a request, selecting one of eight photographs to request a corresponding activity, or using a rather sophisticated electronic communication display with 50 or more pictures, photographs, line drawings, words and/ or other symbols to meet many of their daily communication demands. There are dozens of communication devices available; the identification of the 'right' system for a particular individual requires a comprehensive AAC evaluation by trained professionals. It is essential to match each individual's skills, capabilities, and immediate as well as long range needs to what is available and what is necessary to implement them effectively, using a process referred to as feature matching.

As indicated earlier, most children with AS, particularly those with deletions, do not acquire functional speech. Many parents report their child used words such as "mama" and "more" early on but these words later dropped out. Individuals' difficulties acquiring speech result from a combination of factors that include motor problems, such as low tone in the oral area, structural anomalies such as a protruding tongue; intellectual disabilities, and possible apraxia. Efforts to teach speech to children with deletions have in most cases yielded marginal gains. Those presenting different genetic mechanisms offer better but still guarded prognoses. While no such investigations have been conducted on individuals with AS, those involving other populations have consistently found AAC does not hinder the development of speech. To the contrary, speech is generally fostered following introduction of AAC. It is extremely important to introduce AAC instruction as early as possible in conjunction with other early intervention services. There have been several reports of individuals with AS demonstrating stronger abilities comprehending language than producing it. For example, many individuals have been reported able to understand simple commands and sentences even though they are unable to express such content. However variations appear in the literature, with some investigators failing to note consistent differences in individuals' production vs. comprehension of language. Analyses of expressive language have



demonstrated individuals with AS most often use language to mand (i.e. request desired objects and activities and/or reject undesired ones). Instances of tacting (e.g. labeling and describing) and echoing (i.e. imitation) are rare. The difficulty with imitation suggests a need to proceed cautiously when relying on this method to teach communication and related skills.

While all individuals with AS experience difficulties with communication, the severity of these problems vary greatly among individuals with the same or different underlying genetic mechanisms. It is thus essential to maintain high expectations and give all individuals every opportunity to communicate. Communication skills can be maximized by early and ongoing interventions, including those carried out by experts in AAC. Interventions should target enabling individuals to communicate more effectively with a broad range of partners in various natural settings. A child's ability to communicate with his speech- language pathologist in a therapy room has little significance compared to the child's ability to demonstrate this same skill with teachers and peers in classrooms, playgrounds and other settings. Communication services are best implemented through a combination of direct therapy and consultation. Direct therapy should always be accompanied by systematic probes designed to verify skills observed in therapy are generalizing to other settings as well. For example, an SLP may want to work on turn taking. In addition to direct time spent with the child, the SLP might ask the student's Aide to monitor and collect data on the child's application of this skill (i.e. turn taking) when she has opportunities and reasons to use it in real-life situations. For example, does the student wait her turn in going up to the blackboard? Does she wait her turn as objects are passed from one child to the next during circle time? Does she wait her turn as she stands in line and passes through the food line in the school cafeteria? Similarly, the SLP might teach the student to reject unwanted objects by gently pushing them away. The SLP would collaborate with the Aide and others to identify reasons and opportunities for the student to use this skill naturally and monitor whether or not the student is indeed doing so. For example, during art class the student might reach for and look at one of several crayons out of her reach. A peer might be asked to purposely offer her a differently colored crayon, setting up an opportunity for the student to push it away and repeat her initial request. (Please refer to the 'Education' section of this document for additional examples, and references, of how communication and other related skills can be integrated across the curriculum and throughout the school day).

In summary, it is essential that speech-language pathologists, parents, teachers, peers, employers and others collaborate to maximize individuals' abilities to communicate functionally and thus participate actively in their communities. Children need multiple means of communication and knowledge of when to use one method vs. another depending on particular situations. Educators must understand that communication instruction must not be reserved for therapy rooms but should instead be targeted throughout the day. Themes such as membership, participation, and inclusion should be pervasive in all attempts to foster communication skills. It is through communication that children will establish and maintain friendships and networks of support that will be available throughout their lives.



### Sleep Disorders

Parent reports and recent studies indicate that decreased need for sleep and abnormal sleep/wake cycles are common in AS. An AS child, with abnormal sleep/wake cycles, has been reported to benefit from a behavioral treatment program . Administration of a low dose of melatonin one hour before bedtime has also been shown to be of help in some children but this should not be given in the middle of the night if the child awakens. Use of sedatives such a chloral hydrate or diphenylhydramine (Benadryl) may be helpful if wakefulness excessively disrupts home life. Some families construct safe but confining bedrooms to accommodate disruptive nighttime wakefulness. There are also many AS infants and children who apparently sleep fairly well and do not receive any sleep-related medications.

#### Sexuality

During adolescence, puberty may be delayed by 1-3 years but sexual maturation occurs with normal development of secondary sexual characteristics. Postpubertal females with AS are fertile and pregnancy has been reported. The main issues associated with sexual development in normal individuals have an important component as well in the lives of those with AS. The general approach to consideration of sexual issues in the AS is to recognize the sexual development will occur in a relatively normal physiologic manner for both young men and young women. Accordingly, issues of potential sexual abuse, normal masturbation behaviors, approach to contraception, and access to gynecological care are some of the issues of importance. Sexual education is problematic but important to the child with AS. Educational themes might address emphasis on body parts and on private and public components, differences between boys and girls, issues of how babies are made, understandings regarding acceptable social behaviors, and continued reinforcements and instruction about relationship boundaries. Individuals with developmental handicaps are at increased risk for sexual assault and abuse, and parents should be alert to this and focus on prevention. Boundary issues are particularly difficult in some individuals with AS because of their outgoing personality and fondness of hugging or otherwise wanting to be close to others. Since seizures are known to be affected by a menstrual periods, some individuals may require adjustment of seizure medications. Providing medical contraception may be important in some situations. For females, the contraceptive methods are the ones employed in the normal population and may involve oral contraceptives or progesterone only injections (Depo-Provera shot given once every three months) and other methods. Currently there is no report of a male with Angelman reported to have conceived a child although it appears that that is theoretically possible. Gynecological care is advisable by age 21 years to include a breast and pelvic examination. If a pelvic exam is not possible, ultrasound of pelvic organs may be indicated. Menstrual hygiene is a concern and education should stress identifying body parts, hygienic habits such as washing hands, and of course this must be done in the most basic way due to the cognitive impairments of those with AS.