Medical Issues

Seizures

More than 90% of individuals with AS are reported to have seizures but this may be an overestimate because medical reports tend to dwell on the more severe cases. Less than 25% develop seizures before 12 months of age. Most have onset before 3 years, but occurrence in older children or in teenagers is not exceptional. The seizures can be of any type (i.e. major motor involving jerking of all extremities; absence type involving brief periods of lack of awareness), and may require multiple anticonvulsant medications. Seizures may be difficult to recognize or distinguish from the child's usual tremulousness, hyperkinetic limb movements or attention deficits. The typical EEG is often more abnormal than expected from the clinical appearance, and it may suggest seizures when in fact there are none. There is no agreement as to the optimal seizure medication although valproic acid (Depakote), topiramate (Topamax), lamotrigine (Lamictal), levetiracetam (Keppra), and clonazepam (Klonopin) are more commonly used in the North Amereica. Carbamazepine (Tegretol), ethosuximide (Zarontin), phenytoin (Dilantin), phenobarbital, and ACTH are less commonly used. Vigabatrin (Sabril), an inhibitor of GABA metabolism, should not be used. Single medication use is preferred but seizure breakthrough is common. Some children with uncontrollable seizures have been placed on a ketogenic diet, and this may be helpful in some cases. Children with AS are at risk for medication over-treatment because their movement abnormalities or attention deficits can be mistaken for seizures and because EEG abnormalities can persist even when seizures are controlled.

Central Nervous System Structure

Individuals with AS are generally thought to have normal imaging studies although occasional abnormalities have been reported that probably are coincidental findings. The most common MRI or CT change, when any is detected, is mild cortical atrophy (i.e. a small decrease in the thickness of the cortex of the cerebrum) and/or mildly decreased myelination (i.e. the more central parts of the brain appear to have a slight degree of diminished white matter). Several detailed microscopic and chemical studies of the brain in AS have been reported but the findings generally have been nonspecific or the number of cases has been too few to make meaningful conclusions.

A recent study using advanced neuroimaging techniques (diffusion tensor imaging [DTI], quantitative magnetic resonance imaging [MRI], and magnetization transfer ratio [MTR] imaging) revealed abnormalities in deletion positive individuals with AS. The DTI studies reveal significant differences between AS patients and controls for white matter pathways involving the frontal, temporal, parietal, and limbic areas. Those with AS had reduced white matter fiber density and coherence in these respective regions. Results of MTR, a measure of white matter integrity, showed differences between individuals with AS and controls in the global pallidus, thalamus, frontal white matter, and left temporal regions. Differences in

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

these regions appear to correlate with the language, cognitive, motor, and behavioral difficulties associated with AS. Quantitative MRI study, after controlling for total brain size, showed that those with AS had reduced white matter volumes in the cerebellum, cerebrum, hippocampus, accumbens, caudate, and corpus callosum. There was also subtle cortical thinning in gray matter in temporal, frontal, and occipital regions, primarily in the left hemisphere. The same regions are associated with increased cortical folding/gyrification. Findings in these regions appear to correlate with the clinical/behavioral anomalies (e.g., reduced hippocampal volume corresponds to lower cognitive and memory skills, reduced cerebellar volume corresponds to increased stereotypic behaviors, reduced fiber density and coherence in limbic regions corresponds to impairments in social communication and play). These findings demonstrate that deletion positive AS patients exhibit microstructural changes in white matter fiber tracts that affect the development, wiring, and targeting of axons that link affected brain regions. They also exhibit reduced volume in brain regions that appeared to contribute to the clinical phenotype observed. It has not yet been determined if these abnormalities are present in other molecular subtypes of AS but it seems reasonable to expect that they will be.

Gastrointestinal Issues and Oral-motor Behaviors

Feeding problems are frequent but not generally severe and usually manifest early as difficulty in sucking or swallowing. Tongue movements may be uncoordinated with thrusting and generalized oral- motor incoordination. There may be trouble initiating sucking and ustaining breast feeding, and bottle feeding may prove easier. Frequent spitting up may be interpreted as formula intolerance orgastroesophageal reflux. The feeding difficulties often first present to the physician as a problem of poor weight gain or as a ""failure to thrive"" concern. Infrequently, severe gastroesophageal reflux may require surgery.

AS children are notorious for putting everything in their mouths. In early infancy, hand sucking (and sometimes foot sucking) is frequent. Later, most exploratory play is by oral manipulation and chewing. The tongue appears to be of normal shape and size, but in 30-50%, persistent tongue protrusion is a distinctive feature. Some have constant protrusion and drooling while others have protrusion that is noticeable only during laughter. Some infants with protrusion eventually have no noticeable problem during later childhood (some seem to improve after oral-motor therapy). For the usual AS child with protruding tongue behavior, the problem remains throughout childhood and can persist into adulthood. Drooling is frequently a persistent problem, often requiring bibs. Use of medications such as scopolamine to dry secretions usually does not provide an adequate long term effect. Surgical procedures to ameliorate drooling are possible but apparently rarely used in AS.

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Gait and Movement Disorders

Hyperkinetic movements of the trunk and limbs have been noted in early infancy and jitteriness or tremulousness may be present in the first 6 months of life. Voluntary movements are often irregular, varying from slight jerkiness to uncoordinated coarse movements that prevent walking, feeding, and reaching for objects. Gross motor milestones are delayed; sitting usually occurring after age 12 months and walking often delayed until age 3 to 5 years. In early childhood, the mildly impaired child can have almost normal walking. There may be only mild toe-walking or an apparent prancing gait. This may be accompanied by a tendency to lean or lurch forward. The tendency to lean forward is accentuated during running and, in addition, the arms are held uplifted. For these children, balance and coordination does not appear to be a major problem. More severely affected children can be very stiff and robot-like or extremely shaky and jerky when walking. Although they can crawl fairly effectively, they may ""freeze up"" or appear to become anxious when placed in the standing position. The legs are kept wide-based and the feet are flat and turned outward. This, accompanied by uplifted arms, flexed elbows and downward turned hands, produces the characteristic gait of AS. Some children are so ataxic and jerky that walking is not possible until they are older and better able to compensate motorically for the jerkiness; about 10% may fail to achieve walking. In situations where AS has not been diagnosed, the nonspecific diagnosis of cerebral palsy is often given to account for the abnormal walking. Physical therapy is helpful in improving ambulation and sometimes bracing or surgical intervention may be needed to properly align the legs.

Surgical Procedures and Anesthesia

There are several literature reports of individuals with AS undergoing general anesthesia without any difficulties. Also, the experience reported by many parents on the web and from parent meetings is generally favorable regarding successful general anesthesia and other aspects of surgical intervention. Some scientific reports mention concern for those who have the deletion mechanism (present in 70% of those with AS) because these individuals also have a deletion of GABA receptor genes which are known to be targets of certain anesthetic agents such as benzodiazepines and halogenated ethers. However, the weight of experience thus far indicates that individuals with AS tolerate anesthetic agents well. Convalescence from surgical procedures also appears to occur relatively normally. For example, rather significant surgical interventions of scoliosis repair with rod replacement and bone grafting is not uncommon to be well tolerated in those with AS. There have been recent reports of bradycardia in individuals with AS and the presumption has been that these rhythm problems were due to increased activity of the vagus nerve. These reports are somewhat difficult to interpret because of the complexities associated with hospitalization such as multiple medication use and the variables of the surgical procedure. At this point, it seems unclear if individuals with AS have an increased risk for cardiac rhythm disturbances. Anesthesiologist should certainly be aware of these case reports however and of the

possibility that agents that increase vagal tone may not be well tolerated in individuals with AS.

A final note should be made about seizures since precautions are always advised whenever someone with a seizure disorder undergoes general anesthesia or undergoes any type of operative procedure. At this point, it appears that the usual precautions that would be given for anyone with a seizure disorder would as well apply to someone with AS. The surgical procedure or the anesthesia event itself does not necessarily lead to an exacerbation of seizures and AS. This is not to say that a surgical procedure will not be complicated by the onset of seizures since that is always a possibility and it is generally known that significant health events predispose to exacerbation of seizures whether one has AS or any other type of seizure condition.

Temperature Sensitivity?

Increased sensitivity to outdoor or indoor temperatures has been mentioned on web chat sites and at AS parent meetings. These problems include apparent increased warmth to the skin or increased irritability and hyperactivity when a child with AS is in a warm room or in a room without air conditioning. In these situations, a bona fide fever (e.g., high core body temperature) is rarely ever observed. Individuals with AS appear to sweat normally and thus it appears that they are able to adequately cool themselves. It may be that the apparent increased sensitivity to heat is the result of a neuro-vascular or neuro-sensory phenomenon that affects only the microcirculation of the skin surface. This is only speculation however. At this time it seems fair to conclude that those with AS may have increased sensitivity to heat but it is uncertain if this is a problem unique to AS or if it is something observed in other conditions involving developmental delay.

Occasionally, a hypothermia event has been noted, often in the context of multiple medication use or associated with a common medical illness. In these observances, the core body temperature has been documented to be abnormally low. In these cases (which are very rare) it appears that the hypothermia is not a recurrent or chronic problem and it usually resolves in a day or two.

Physical Growth

Newborns appear to be physically well formed, but by 12 months of age some show a deceleration ofcranial growth which may lead to relative or absolute microcephaly (absolute microcephaly means having a head circumference in the lower 2.5 percentile). The prevalence of absolute microcephaly varies from 88% to 34% and may be as low as 25% when non-deletion cases are also included. Most AS individuals however have head circumferences less than the 25th percentile by age 3 years, often accompanied by a flattened back of the head. Average height is lower than the mean for normal children but

most AS children will plot within the normal range. Final adult height has ranged from 4 foot 9 inches to 5 foot 10 inches in a series of 8 adults with AS. Familial factors will influence growth so that taller parents have AS children that tend to be taller than the average AS child. During infancy weight gain may be slow due to feeding problems but by early childhood most AS children appear to have near normal subcutaneous fat. In later childhood obesity can occur. Food-related behaviors (e.g., eating non-food items, apparent increased appetite, increased behavioral orientation to food) are common in AS and may contribute to obesity onset. Some weight gain can occur during young adulthood and obesity can be a management concern. Severe (e.g., morbid) obesity is a very uncommon occurrence in AS.

Hypopigmentation, Strabismus and Ocular Albinism

When AS is caused by the large deletion, skin and eye hypopigmentation usually result. This occurs because there is a pigment gene (the P gene, also termed OCA2), located close to the AS gene, that is also missing. This pigment gene produces a protein that is believed to be crucial in melanin synthesis. Melanin is the main pigment molecule in our skin. In some children with AS, this hypopigmentation can be so severe that a form of albinism is suspected. When AS is caused by the other genetic mechanisms, this gene is not missing and thus normal skin and eye pigmentation is seen. Children with AS who have hypopigmentation are sun sensitive, so use of a protective sun screen is important. Not all AS children with deletions of the P gene are obviously hypopigmented, but may only have relatively lighter skin color than either parent. Surveys of individuals with AS demonstrate an increased incidence of strabismus. This problem appears to be more common in children with hypopigmentation (as above), since pigment in the retina is crucial to normal development of the optic nerve pathways. Management of strabismus in AS is similar to that in other children: evaluation by an ophthalmologist, correction of any visual deficit, and where appropriate, patching and surgical adjustment of the extraocular muscles. The hypermotoric activities of some AS children will make wearing of patches or glasses difficult but many are able to accomplish this.

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