Health Watch Table — Angelman Syndrome (AS)

Forster-Gibson, Berg and Korossy 2015

About Angelman syndrome:

Neurogenetic disorder due to lack of expression of a gene on the maternally inherited chromosome 15q11-q13. Physical features include delayed motor milestones, movement or balance disorders and ataxic gait, severe intellectual developmental delay, limited or absent speech, seizures, sleep disturbances, characteristic facial features and distinctive EEG pattern. Behaviour characteristics, include apparent bouts of excessive, often inappropriate laughter (contributing to an impression of happy demeanor), easy excitability, repetitive or stereotyped behaviours (such as hand flapping and mouthing) and hypermotoric behaviour [1-3]

Video overview of AS produced by Angelman Foundation (the Netherlands), in Dutch. For English subtitles, place cursor on 'cc' on menu bar below screen and select "on":
www.youtube.com/watch?feature=player_detailpage&v=RHastPSc9XQ

Note: This health watch table (HWT) was developed for use with the *Primary care of adults with developmental disabilities: Canadian consensus guidelines*[4] and associated set of tools[5] which focus on health care specific to individuals with developmental disabilities. The guideline number will be referenced in the table if applicable to individuals with AS.

CONSIDERATIONS	RECOMMENDATIONS
1. HEENT (HEAD, EYES, EARS, NOSE, THROAT)	
Children & Adults: Strabismus and refractive errors (hyperopia, astigmatism and myopia) are common [6]	☐ Arrange ophthalmology assessment at diagnosis, then every 2 years.
Keratoconus, leading to visual distortion, associated with frequent eye-rubbing, can present in adulthood[7]	☐ Explore underlying cause for eye rubbing if present. Behavioural therapy may be helpful to discourage eye rubbing if there is concern about damage to the eye. [9]
Otitis media is relatively common in young children, and can manifest as head banging or other self-injurious behaviour	☐ Screen for otitis media, especially in childhood and in the presence of recent-onset self-injurious behaviour.
High rates of swallowing/ choking/ aspiration episodes, associated with eating, and gagging, unrelated to eating, have been reported [8]	☐ Consider referral for a swallowing study, or, if not feasible, alert caregivers to possible occurrence of pneumonia due to aspiration risk.
2. DENTAL	
Children & Adults: Dental related problems (e.g., widely-spaced teeth, drooling, teeth grinding, excessive chewing/mouthing [possibly associated with GERD – see GI below] are common.	☐ Ensure adherence to good oral hygiene and regular preventive dental evaluation and treatment practices. ☐ Consider medications (carefully administered) and surgical intervention for excessive drooling, each of which has been associated with variable degrees of success.
3. GASTROINTESTINAL	
Children: Feeding problems – typically, sucking and swallowing difficulties, due to hypotonia, are common in infants Constipation (often due to reduced fluid intake) and GERD are common Obesity, with onset typically in	☐ Evaluate feeding problems and monitor weight gain carefully. Refer for feeding and nutritional management if underweight. Consider including possibly beneficial occupational therapy in management strategy to improve fine motor and oral motor control. ☐ Ensure adequate fluid and fiber intake and consider management strategies, especially PEG 3350, recently recognized as an effective and well-tolerated medication choice for constipation. [10]; evaluate and treat GERD as per DD guidelines (#15)[4];

© Surrey Place Centre 2015

CONSIDERATIONS	RECOMMENDATIONS
adolescence, may occur, often due to overeating [possibly associated with limited sense of fullness] and lack of exercise, particularly in children with AS caused by paternal uniparental disomy (pUPD) (see section 11 – Other, below)	☐ Consider referral to dietician, if overweight.
Adults: GERD and constipation are common. Obesity may occur	☐ Evaluate and treat as described for children above.
4. ENDOCRINE & SEXUALITY	
Children Puberty and development of secondary sexual characteristics, while normal, may be delayed from 1 to 3 years.	☐ Ascertain status and discuss menstrual management.
Adults: Both genders are presumed to be fertile Women are vulnerable to sexual abuse, sexually transmitted disease and unwanted pregnancy (see DD guidelines #6)[4] Individuals of both genders may engage in masturbation	☐ Recommend genetic counseling for family members. (Also see #11 – Other, below.) ☐ While contraception may be requested to avoid unwanted pregnancy, it may increase the potential for sexual abuse. ☐ Recommend behaviour therapy to deal with masturbation.
5. MUSCULOSKELETAL	
Children & Adults: All have some degree of movement or balance disorder, most characteristically jerky movements, ataxic, wide-based, stiff-legged gait with arms flexed; ~10% may never walk Hypotonia in ~50% during infancy may persist in ~20%; ~30% develop hypertonia Ankles may sublux or pronate Contractures may develop Scoliosis is common, occurring in ~20% of children and over 50% of adults Cardiorespiratory compromise may occur and should be considered in individuals who develop severe scoliosis Osteopenia/osteoporosis may develop in early adulthood due to reduced mobility and chronic antiepileptic treatment (see #6 below and DD guidelines #17)[4]	☐ Refer to physiotherapist and occupational therapist for advice on posture and seating from time to time, and throughout adulthood; promote lifelong physical activity (hippotherapy and swimming are frequently-mentioned preferred recreational activities) and use of adaptive devices to maintain mobility and independence.[11] ☐ Undertake regular evaluation for scoliosis in children (especially during pubertal growth spurt) and adults; refer to orthopedics for consideration of bracing or surgery.
6. NEUROLOGY	
Children & Adults: ~ 90% have history of seizures and characteristic, abnormal EEG findings (even when seizures are controlled) Onset of seizures usually <3 years, but	☐ Arrange neurology referral to ensure appropriate comprehensive initial appraisal (including MRI and EEG investigation), regular monitoring of seizure medications and periodic consideration of discontinuation after 2 seizure-free years. The latter should be a joint decision between

CONSIDERATIONS	RECOMMENDATIONS
can be later Seizure control in some individuals (~10%) may not be achieved Optimal medication use has been described by Clayton-Smith [12] Movement abnormalities, such as ataxia and tremors (extended and disabling tremulousness or tremor, present in teens and adults)[13], may be mistaken for seizures, potentially leading to medication overuse Some anticonvulsants (carbamezapine and vigabatrin) may exacerbate seizures	parents/care providers and the neurologist[12]
Long-term use of anti-convulsants increases risk of osteopenia and osteoporosis	☐ Screen early and regularly for osteopenia/osteoporosis in individuals on long-term use of anti-convulsants. ☐ Refer to osteoporosis specialist if situation warrants.
7. MENTAL HEALTH/BEHAVIOURAL	
Children & Adults: Frequent laughter (often inappropriate), apparent happy demeanour, easy excitability, hyperactivity, sleep disturbance (e.g., night awakenings, obstructive sleep apnea), and aggressive behaviours such as grabbing and pulling, but not self-injury, are common [14] Interventions based on applied behavior analysis (ABA) are being used to teach adaptive and communication skills to improve individuals' functioning and address behaviours that challenge services www.angelmanbehaviors.org	☐ Arrange consultation surrounding hyperactivity, in the first instance with and Occupational Therapist (OT for sensory issues, a Behaviour Therapist (BT) and then with a psychiatrist to consider medication management for hyperactivity, keeping in mind that the patient may have an atypical response to stimulant medication. ☐ Recommend implementation of consistent nighttime routine and other helpful strategies outlined by Clayton-Smith [12] to improve sleep habits. ☐ Consider a trial of melatonin (sourced in a pharmacy, not a health food store), which has been used with some success for sleep disorders in small samples of individuals, combined with behavioural interventions. ☐ Consider referral to a sleep specialist or clinic. ☐ If behaviour changes/occur, evaluate for medical cause (e.g., otitis media, GERD, UTI/dental abscess). Also see DD guidelines #22[4]
Language development is variably, though markedly impaired – majority do not develop speech; receptive language skills are always more advanced than expressive language skills and continue to improve even in adulthood	☐ Early and ongoing intervention by speech-language therapist is essential and should focus on nonverbal methods of communication. Use of augmentative communication aids, such as picture cards or communication boards, should be encouraged.
Emotional needs are often neglected in severe disability combined with limited communication	☐ "Work with the individual and family to optimize opportunities for inclusion, participation and friendship". [see our *Health Watch Table – Autism Spectrum Disorder (ASD), section 8,* at www.surreyplace.on.ca/Documents/HWT_ASD.pdf

Note: There is a divergence of opinion on the diagnosis of autism spectrum disorder (ASD) in Angelman syndrome, with some studies showing a high percentage of individuals with this condition scoring above autism cutoff on the Autism Diagnostic Observation Schedule (ADOS).[15-18] Examples of behaviours in Angelman syndrome consistent with ASD diagnosis include repetitive or stereotyped movements and fascination with water. Please see our *Health Watch Table – Autism Spectrum Disorder (ASD)* at www.surreyplace.on.ca/Documents/HWT_ASD.pdf for details concerning diagnosis and management of ASD
Diagnosis of ASD may be important in order for individuals to gain access to specialized services

CONSIDERATIONS	RECOMMENDATIONS
8. INFECTIOUS DISEASE/IMMUNIZATION	
☐ Follow DD guidelines (#20) for routine immunization.	
9. OTHER	
Children & Adults: Genetic diagnosis can be made in 85-90% of cases Four known molecular mechanisms can disrupt expression of the maternal UBE3A gene, causing Angelman syndrome [19]: -deletion 15q11-q13 region of the maternally derived #15 [70%] -paternal uniparental disomy [pUPD] [2-3%] -imprinting defects [3-5%] -mutations in the *UBE3A* gene lacking the maternal methylation pattern [10%] These different underlying molecular mechanisms result in variability in cognitive, language and motor features of Angelman syndrome - del15q11-q13 is associated with most severe and imprinting defects/UPD with less severe impairments. Hypopigmentation (hair, skin) occurs in individuals with deletion (sometimes encompassing the OCA2 gene) and overweight/obesity in individuals with UPD)	☐ If diagnosis is clinically suspected, refer to genetic centre for aetiologic investigation. ☐ Since the recurrence risk varies with the genetic mechanism leading to disruption of UBE3A, accurate genetic testing of the individual with Angelman syndrome is imperative in order to provide accurate genetic counseling to all family members, including first and second degree relatives. ☐ Ensure that genetic counseling has addressed fertility and recurrence risk issues in the individual with Angelman syndrome
The family physician can play an important advocacy role in ensuring that life-long supports, including special education in childhood and teenage years as well as close medical supervision are in place for individuals with Angelman syndrome.	
10. CAREGIVER AND PROFESSIONAL RESOURCES	
Canadian Angelman Syndrome Society: http://www.angelmancanada.org/	
Angelman Syndrome Foundation: http://www.angelman.org/	
ASSERT Angelman Syndrome Support Education and Research Trust; http://www.angelmanuk.org/index.html	

REFERENCES CITED

1. Williams CA, Beaudet AL, Clayton-Smith J, Knoll JH, Kyllerman M, Laan LA, et al. Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet A. 2006 Mar 1;140(5):413-8. Available from: http://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.31074/pdf.

2. Walz NC. Parent report of stereotyped behaviors, social interaction, and developmental disturbances in individuals with Angelman syndrome. J Autism Dev Disord. 2007 May;37(5):940-7.

3. Thibert RL, Larson AM, Hsieh DT, Raby AR, Thiele EA. Neurologic manifestations of Angelman syndrome. Pediatr Neurol. 2013;48(4):271-9.

4. Sullivan WF, Berg JM, Bradley E, Cheetham T, Denton R, Heng J, et al. Primary care of adults with developmental disabilities: Canadian consensus guidelines. Can Fam Physician. 2011 May;57(5):541-53. Available from: http://www.cfp.ca/content/57/5/541.full.pdf+html.

© Surrey Place Centre 2015

5. Developmental Disabilities Primary Care Initiative. *Tools for the primary care of people with developmental disabilities.* Toronto: MUMS Guideline Clearing House; 2011. Available from: http://www.surreyplace.on.ca/primary-care?id=135.

6. Michieletto P, Bonanni P, Pensiero S. Ophthalmic findings in Angelman syndrome. J AAPOS. 2011 Apr;15(2):158-61.

7. Laan LAEM, Haeringen AV, Brouwer OF. Angelman syndrome: A review of clinical and genetic aspects; 10536901. Clin Neurol Neurosurg. 1999;101(3):161-70.

8. Larson AM, Shinnick JE, Shaaya EA, Thiele EA, Thibert RL. Angelman syndrome in adulthood. Am J Med Genet A. 2015 Feb;167(2):331-44.

9. Dagli AI, Williams CA. Angelman syndrome [Management section]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews [internet]. Seattle: University of Washington; 1998 [Updated 2015 May 14]. . Available from: http://www.ncbi.nlm.nih.gov/books/NBK1144/. Accessed 9 Sep 2015.

10. Rowan-Legg A, Canadian Paediatric Society, Community Paediatrics Committee. Managing functional constipation in children. Paediatr Child Health. 2011 Dec;16(10):661-70. Available from: http://www.cps.ca/documents/position/functional-constipation.

11. Williams CA, Sarika U. Peters and Stephen N. Calculator. *Facts about Angelman syndrome.* Angelman Syndrome Foundation; 2009. Available from: http://www.angelman.org/_angelman/assets/File/facts%20about%20as%202009%203-19-10.pdf. Accessed 2 June 2014.

12. Clayton-Smith J and DYSCERNE - Angelman Syndrome Guideline Development Group. *Management of Angelman syndrome: a clinical guideline.* DYSCERNE A Network of Centres of Expertise in Dysmorphology; 2011. Available from: https://www.orpha.net/data/patho/Pro/en/AngelmanGuidelines2011.pdf. Accessed 8 Mar 2014.

13. Dagli A, Buiting K, Williams CA. Molecular and Clinical aspects of Angelman syndrome. Mol Syndromol. 2012 Apr;2(3-5):100-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3366701/.

14. Oliver C, Adams D, Allen D, Bull L, Heald M, Moss J, et al. Causal Models of Clinically Significant Behaviors in Angelman, Cornelia de Lange, Prader-Willi and Smith-Magenis Syndromes. Int Rev Res Dev Disabil. 2013;44:169-211.

15. Mertz LG, Thaulov P, Trillingsgaard A, Christensen R, Vogel I, Hertz JM, et al. Neurodevelopmental outcome in Angelman syndrome: Genotype-phenotype correlations. Res Dev Disabil. 2014 Jul;35(7):1742-7.

16. Peters SU, Horowitz L, Barbieri-Welge R, Taylor JL, Hundley RJ. Longitudinal follow-up of autism spectrum features and sensory behaviors in Angelman syndrome by deletion class. J Child Psychol Psychiatry Allied Discip. 2012;53(2):152-9.

17. Dan B. Behaviour. In: Dan B, editor. Angelman syndrome. London, UK: Mac Keith Press; 2008. p. 63-74.

18. Pelc K, Cheron G, Dan B. Behavior and neuropsychiatric manifestations in Angelman syndrome. Neuropsychiatr Dis Treat. 2008;4(3):577-84.

19. Bird LM. Angelman syndrome: Review of clinical and molecular aspects. Application of Clinical Genetics. 2014;7:93-104.

PUBLISHED HEALTH CARE GUIDELINES REVIEWED AND COMPARED

Clayton-Smith J. Angelman syndrome. J Pediatr Neurol. 2010;8(1):97-9.

Clayton-Smith J and DYSCERNE - Angelman Syndrome Guideline Development Group. *Management of Angelman syndrome: a clinical guideline.* DYSCERNE A Network of Centres of Expertise in Dysmorphology; 2011. Available from: https://www.orpha.net/data/patho/Pro/en/AngelmanGuidelines2011.pdf. Accessed 8 Mar 2014.

Coppola G, Verrotti A, Mainolfi C, Auricchio G, Fortunato D, Operto FF, et al. Bone mineral density in Angelman syndrome. Pediatr Neurol. 2007 Dec;37(6):411-6.

Dagli AI, Williams CA. Angelman syndrome [Management section]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews [internet]. Seattle: University of Washington; 1998 [Updated 2015 May 14]. . Available from: http://www.ncbi.nlm.nih.gov/books/NBK1144/. Accessed 9 Sep 2015.

Dan B. Angelman Syndrome. London, UK: Mac Keith Press; 2008.

Dan B. Angelman syndrome: current understanding and research prospects. Epilepsia. 2009 Nov;50(11):2331-9.

Didden R, Korzilius H, Duker P, Curfs L. Communicative functioning in individuals with Angelman syndrome: a comparative study. Disabil Rehabil. 2004 Nov 4-18;26(21-22):1263-7.

Didden R, Sigafoos J, Korzilius H, Baas A, Lancioni GE, O'Reilly MF, et al. Form and function of communicative behaviours in individuals with Angelman syndrome. Journal of Applied Research in Intellectual Disabilities. 2009 Nov;22(6):526-37.

Dykens EM, Hodapp RM, Finucane BM. Angelman Syndrome. In: Genetics and mental retardation syndromes : a new look at behavior and interventions. Baltimore: Paul H. Brookes Pub. Co.; 2000. p. 226-33.

Guerrini R, Carrozzo R, Rinaldi R, Bonanni P. Angelman syndrome: etiology, clinical features, diagnosis, and management of symptoms. Paediatr Drugs. 2003;5(10):647-61.

Lennox N, Developmental Disability Steering Group. Angelman syndrome. In: Lennox N, Developmental Disability Steering Group, editors. Management guidelines: developmental disability. version 2, 2005 ed. Melbourne: Therapeutic Guidelines; 2005. p. 285-7.

Murakami C, Nahas Pires Correa MS, Nahas Pires Correa F, Nahas Pires Correa JP. Dental treatment of children with Angelman syndrome: a case report. Spec Care Dentist. 2008 Jan-Feb;28(1):8-11.

Pelc K, Boyd SG, Cheron G, Dan B. Epilepsy in Angelman syndrome. Seizure. 2008 Apr;17(3):211-7.

Pelc K, Cheron G, Boyd SG, Dan B. Are there distinctive sleep problems in Angelman syndrome? Sleep Med. 2008 May;9(4):434-41.

Van Buggenhout G, Fryns JP. Angelman syndrome (AS, MIM 105830). Eur J Hum Genet. 2009 Nov;17(11):1367-73.

Williams CA, Dagli A. Angelman Syndrome. In: Cassidy SB, Allanson JE, editors. Management of genetic syndromes. 3rd ed. Hoboken, N.J.: John Wiley & Sons; 2010. p. 69-80.

Williams CA, Discoll DJ, & Dagli A. Clinical and genetic aspects of Angelman Syndrome. Genetics in Medicine. 2010. 12, 385-395.

Developed by: ***Cynthia Forster-Gibson,*** *MD, PhD;* ***Joseph M Berg***[1]*, MB, BCh, FRCPSYCHi, FCCMG;* ***Marika Korossy****, BA.*

We gratefully acknowledge the following Invited Reviewers: **Elspeth Bradley** *MB BS, PhD, FRCPC, FRCPsych* [Developmental Psychiatrist, Canada]; **Esther Bakker-van Gijssel** [Family Physician, The Netherlands

Expert Clinician Reviewer:

Jane Summers Ph.D., C.Psych
Director of Interprofessional Practice
Underserved Populations Program
(Child Youth and Family, Dual Diagnosis, Geriatric Mental Health Services)
Centre for Addiction and Mental Health
1001 Queen Street West
Toronto, Ontario M6J 1H4

About this Health Watch Table

Initial publication:
10 September 2015 Forster-Gibson, Berg, Korossy

Revision history:

Edit history:

[1] We note with great regret that our colleague Joe Berg passed away in July 2013, during early stages of the development of the Angelman syndrome health watch table.