Adult Health Care Issues in the Angelman Syndrome

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Harry Angelman

Syndrome description in 1965



American Journal of Medical Genetics 11:453–468 (1982)

The Angelman ("Happy Puppet") Syndrome

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Literature Reports of Adults with AS

Author	Year	Ages
Williams and Frias	1984	5: 17-33 yrs
Bjerre et al.,	1984	1:75 yrs
Buntinx et al.,	1995	18: >18yrs (5 >35yrs;1: 47 yrs
Reish and King	1995	1:50 yrs
Laan et al.,	1996	28: 20-53 yrs
Van Buggenhout	2000	3:32,49,52 years
Clayton-Smith	2001	28: 16-40 yrs
Harbord	2001	2: 22,43 yrs
Stecker and Myers	2003	1:32 yrs
Philippart	2005	1: 74 yrs
Thomson	2006	34: mean 21.6 yrs (5.3-39 yrs)
	Total cases	122

Laan et al., Am J Med Genet, 1996

TABLE I. Clinical Findings in 28 Adult Angelman Patients Compared to Those in Children as Reported in the Literature

	Adult AS patients	%	AS Children* %
Face			
Macrostomia	28/28	100	
Mandibular prognathism	26/27	96	95
Good visual acuity (without glasses)	20/25	80	89
Strabismus	16/28	57	42
Keratoconus	2/28	7	
Neurological findings			
Limb hypertonicity	26/28	93	
Hyperreflexia	25/28	89	
Tremor	11/13	85	
Epileptic seizures	23/28	82	86
Scoliosis	20/28	71	11
Truncal hypotonia	13/26	50	
Behavior			
Hyperactivity	14/28	50	
Fixation on food	6/18	33	
Obesity	4/27	15	

*Percentages reported by Clayton-Smith [1993] 82 patients, almost all children).

Laan et al., Am J Med Genet, 1996

TABLE II. Daily Life Activities in Adult AS Patients

		%
Love to watch TV	24/24	100
Handle spoon or fork	23/27	85
Ability to express their will to some extent	23/27	85
Understanding of simple commands	22/28	79
Attraction to water	21/27	78
Use of simple gestures (e.g., pointing)	21/27	78
Cooperative in (un)dressing	19/28	68
Ability to walk	17/28	61
Daytime continence for urine	16/28	57
Undress themselves	14/28	50
Dress themselves	3/28	11
Wash themselves	0/28	0

28 Adults with AS

(12 M,16 F; ages 16-40) (19 del 7 UBE3A, 1 imprint, 1 UPD)

Angelman syndrome: evolution of the phenotype in adolescents and adults

J. Clayton-Smith
Dev Med Child Neurol. 2001

• General health good	23
– 7 seizures, 1 esophagitis, 2 scoliosis	
• ↑ seizures after teenage years	8
• Seizures	11
• Reflux	12
• Obesity	9
• Normal puberty	28
• ↓ mobility	28
• ↑ rigidity, contractures	28
• Worsening tremor	7
• ↓ hyperactivity	28
• Able to walk	21
• Able to feed self	20
• Carry out simple home chores	17
• Dry during the day	20

Health Issues in Adulthood from Previous Studies

- Physical health remains relatively good
- Some change in facial features
- Improved attention span
- Seizures may return
- Mobility decreases
  - Tendency to gain weight
  - Scoliosis
    - 40% can develop this
    - ↑ risk during growth spurt
    - Requires surveillance
    - Surgery may be necessary
- Puberty
  - May start relatively late
  - Normal progression through puberty
  - Masturbation
  - Regular menstruation
  - Fertility

Obesity in AS

- Typically has onset during adolescence on in teenage years
- Associated with increased appetite but not as increased as in the Prader-Willi syndrome
- Exacerbated by decreased activity or lack of interest in exercise
- Rarely becomes severe or "morbid"
- May be less common in those with the deletion

Scoliosis in AS

Clayton-Smith, Dev Med Child Neuro, 2001

- 40-60% prevalence in adults with AS
- More common in non-ambulatory
- More prevalent in girls
- Exacerbated by
  - Diminished activity
  - Obesity
  - Contractures
- Some can tolerate bracing
- Surgery is an option

Neuroleptic Medication use in AS

- Rarely used to treat classical disorders in AS (e.g., schizophrenia, bipolar)
- Often used for "off-label" indications:
  - Nighttime wakefulness, restlessness
  - Agitation, aggressiveness, acting out
  - Other disruptive behaviors
- Effectiveness not yet studied in AS

Summary of Neuroleptic Drug Types

Drug	Trade Name	EPS	Weight gain	NMS
Modern "atypical" antipsychotics				
Aripiprazole	Abilify	+	0	?
Clozapine	Clozaril	0	+++	+
Olanzapine	Zyprexa	0	+++	+
Quetiapine	Seroquel	+	+++	+
Risperidone	Risperdal	++	+	+
Ziprasidone	Geodon	+	0	+
Conventional antipsychotics in moderate dose				
Chlorpromazine	Thorazine	+++	+	++
Fluphenazine	Prolixin	+++	+	++
Haloperidol	Haldol	+++	+	++
Loxipine	Loxitane	+++	+	++

EPS = extrapyramidal signs, NMS = neuroleptic malignant sydnrome

Adapted from Gardner et al., CMAJ, 2005

Surgical Procedures in AS

- Many AS individuals undergo surgery with general anesthesia
  - Fundoplicaton, G-tube insertion, scoliosis repair, arthrodeses, cleft lip repair, dental procedures, tracheostomy, etc.
  - Seizure management always a concern
  - Post operative course otherwise appears relatively uncomplicated

Reported Surgical Experience in AS

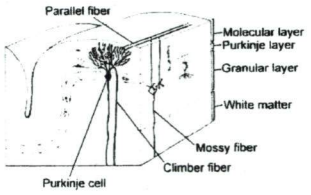
- Bujok and Knapik (Ped Anes, 2004)
  - 12 yr old boy for dental procedure
  - 2 min episode of bradycardia to 40/min
  - Response to atropine was delayed
  - Advise to avoid GABAR interacting agents such as benzodiazepine and limit inhalational halogenated ethers
- Yoshitaka et al, JJDSA, 2005
  - 18 yr male for dental treatment
  - No anesthesia problem
  - Midazolam, thiopental, isoflurane (all affect GABARs)
- Masato K, et al., JJDSA, 2003
  - 2 yr old for adenoidectomy
  - anesthesia with 5% sevoflurane
  - Mild hyperhermia (temp to 37.9)

Anticonvulsant Medication Use

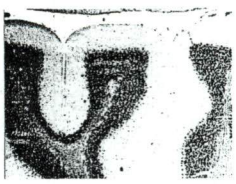
- About 50% use single medications
- Combinations include:
  - Valproate and clonazepam (Klonopin)
  - Valproate and topiramate (Topamax)
  - Valproate and lamotrigine (Lamictal)
  - Others
- Carbamazepine (Tegretol) used infrequently
- Avoid vigabatrin (Sabril), tigabine (Gabitril)

Carbamazepine*	Carbitrol, Tegretol
Clonazepam	Klonopin
Ethosuximide	Zarontin
Hydantion	Dilantin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Oxcarbazepine	Trileptal
Tiagabine*	Gabitril
Topiramate	Topamax
valproic acid	Depakene
zonisamide	Zonegran

Tremors in AS



- Purkinje Cells
  - Main output from cerebellum
  - Extremely large
  - Involved in ataxia and tremor disorders
  - Abnormal function in the UBE3A Angelman mouse (Cheron et al., Neurosci, 2005)



Tremors and rigidity in AS

- Present in almost all with AS
- Varies with emotional state, time of day, fatigue, etc.
- May improve or worsen with anticonvulsants and other drugs
  - Harbord, J Clin Neurosci, 2001: levodopa responsive "Parkinsonism" in a 23 and 43 year old
  - Stecker and Meyers, Clin Neurol Neurosurg, 2003: reserpine responsive myoclonus in 32 year old
- May increase with advancing age
- No obvious relationship to seizures on EEG

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ANGELMAN SYNDROME IN THREE ADULT PATIENTS WITH ATYPICAL PRESENTATION AND SEVERE NEUROLOGICAL COMPLICATIONS

BY G.J.C.M. VAN BUGGENHOUT[1], M.J. DESCHHEMAEKER[2], P. THIRY[1], J.G.M. TROMMELEN[3], R.C.J. HAMEL[1] AND J.P. FRYNS[1]

- PH- 52 yrs
  - Institutionalized since age 7.
  - Slow and rigid boy with slow tremors
  - MRI cerebellar atrophy
  - 27 clumsy walking, sever spasticity, clonus
  - Carbamazepin, valporate, baclofen
  - Non-ambulatory at 52
- KS- 32 yrs
  - Seizures at 2 years, never ambulatory
  - institutionalized since age 6?
  - Severe quadriplegia with contractures, scoliosis age 13 yrs
  - Age 29: change in sleep patterns, fell asleep during the day
  - Medication history not noted
- DVO- 49 yrs
  - institutionalized age 28?
  - Semi-ambulatory at 49
  - Lower limb regidity and spastic walking
  - Day/night sleep patterns disturbed, fell asleep in am
  - History of seizures as child, recurrence at age 29
  - Medication history not noted

Life Span in AS

- Several case reports of relatively long life
- No reports of deaths related to:
  - Diabetes
  - Cancer
  - Autoimmune disorder
  - Neurodegenerative disease
- Life span expected to be decreased more when non-ambulatory and tube fed
- Seizures and cognitive impairment alone do not appear to be obvious risk factors for decreased life span