Neurobehavioral Approaches in Angelman syndrome: Part I

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What you will learn about today

- Talk is organized around:
  - Health Watch Table for Individuals with AS (AS-HWT)
  - On-line Behavior Modules
- Learn how these resources can be used to help individuals with AS receive appropriate care and support to maximize their physical, behavioral and mental health

About Us

- Jane Summers, PhD (psychologist), CAMH in Toronto
- Erick Sell, MD (neurologist), CHEO in Ottawa
- Mutual interest in seeing people with AS
- Neurology + behavior = Neurobehavioral approach
- Clinical aims:
  - Improve physical and emotional health, reduce occurrence of challenging behavior
  - Enable individual with AS to reach full potential, maximize quality of life

Health Watch Table — Angelman Syndrome (AS)
Forster-Gibson, Berg and Korossy 2015

AS Health Watch Table (AS-HWT)

- Developed in 2015 by Cynthia Forster-Gibson, Joseph Berg and Marika Korossy
- Purpose is to provide anticipatory guidance for health/mental health concerns, monitor health/mental health needs across all ages/stages
- Reviews physical and behavioural/mental health issues and provides recommendation or guidance for how to manage them

www.surreyplace.on.ca/documents/Primary%20Care/HWT-AS10Sep2015.pdf

Health Watch Table — Angelman Syndrome (AS)
Forster-Gibson, Berg and Korossy 2015

Areas covered in AS-HWT*

- Genetics
- Neurology
- Musculoskeletal
- HEENT (Head, Eyes, Ears, Nose, Throat)
- Gastrointestinal
- Dental
- Endocrine & Sexuality
- Mental health/behavioral

* We have added our own information in italics

On-Line Behavior Modules

DEVELOPED BY

Angelman Syndrome Foundation

FUNDING PARTNERS

Canadian Angelman Syndrome Society

Fred and Renee Pritzker

- Social and environmental influences on aggressive behavior
- Aggression as a communicative behavior
- Cognitive and sensory issues
- Mental health influences on aggressive behavior
- Neurologic and medical influences on aggressive behavior

www.angelmanbehaviors.org

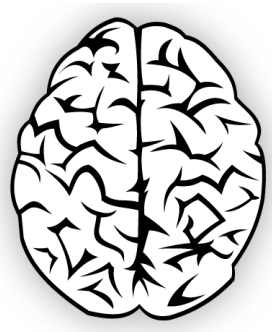
Genetics

- 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 (deletion 15q11-q13; paternal uniparental disomy, imprinting defects, mutation in the UBE3A gene)
- Different underlying molecular mechanisms result in variability in cognitive, language and motor features; deletion 15q11-q13 is associated with most severe and imprinting/UPD with less severe impairments

Genetics
(continued)

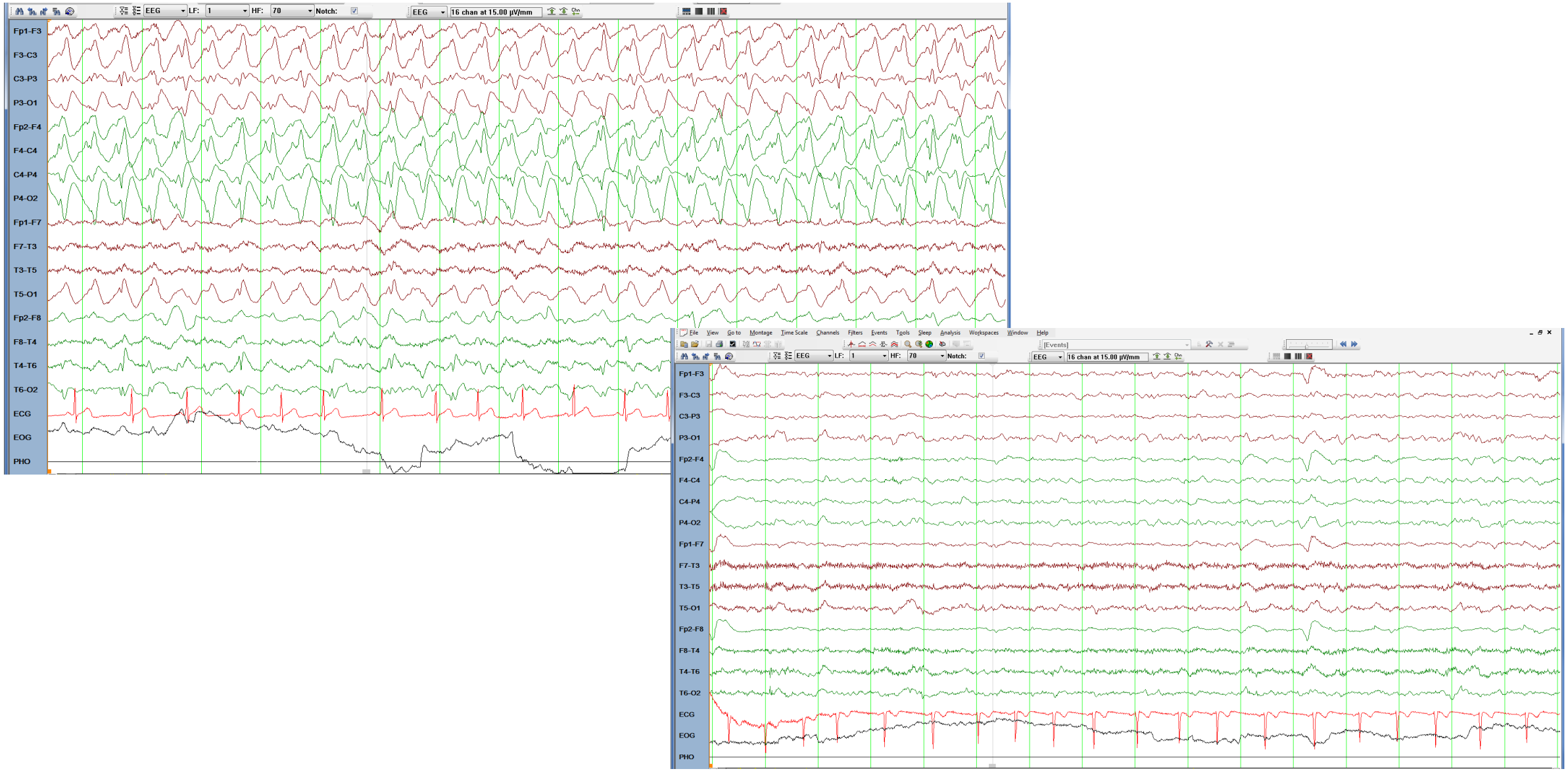
RECOMMENDATIONS: If diagnosis is clinically suspected, refer to genetic centre for etiological evaluation. Accurate testing is imperative in order to provide accurate genetic counselling to all family members, including first and second degree relatives (related to recurrence risk that varies in relation to genetic mechanism leading to disruption of UBE3A).

Neurology

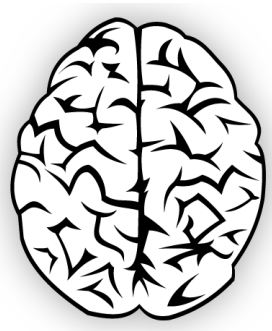


- ~90% have history of seizures and characteristic, abnormal EEG findings (even when seizures are controlled)
- Onset of seizures usually <3 years but can be later. Seizure control in some (~10%) may not be achieved
- Movement abnormalities (ataxia and tremors) may be mistaken for seizures, potentially leading to medication overuse
- Some anticonvulsants may exacerbate seizures
- Long-term use of anti-convulsants increases risk of osteopenia and osteoporosis

Non-convulsive status epilepticus



Neurology (continued)



RECOMMENDATIONS: Arrange neurology appointment to ensure appropriate comprehensive initial appraisal *(EEG often done to better characterize seizures or when encephalopathy; MRI not done routinely).*

Regular monitoring of seizure medications and periodic consideration of discontinuation after 2 seizure-free years. Discontinuation should be a joint decision between parents/careproviders and neurologist.

Screen early and regularly for osteopenia/osteoporosis in individuals on long-term use of anti-convulsants

Refer to osteoporosis specialist if situation warrants

Anticonvulsants

- Clobazam
- Levetiracetam
- Ethosuximide

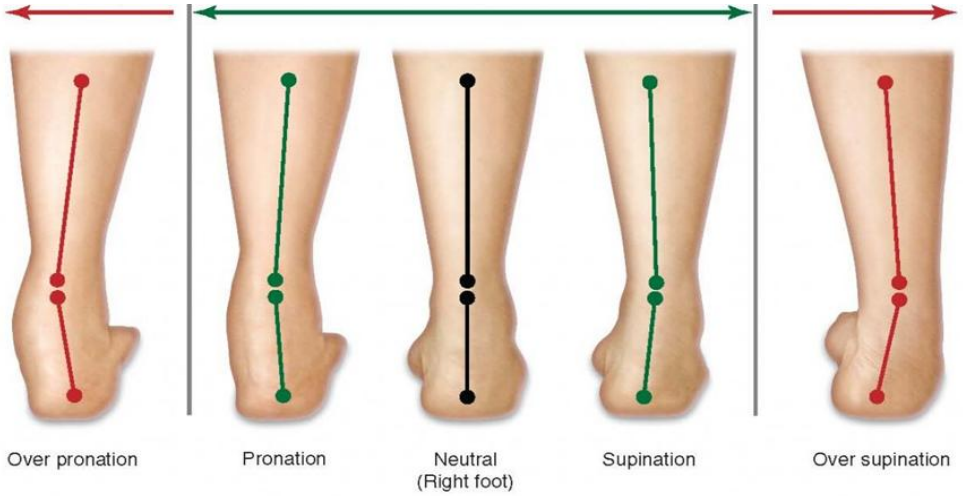
- Lamotrigine
- Topiramate
- clonazepam

- Phenobarbital
- Phenytoin
- Carbamazepine

- Valproate

Musculoskeletal

- All have some degree of movement or balance disorder. Hypotonia and hypertonia may occur. Ankles may sublux or pronate. Contractures may develop.



Musculoskeletal

(continued)

RECOMMENDATIONS: Physiotherapist and occupational therapist for advice on posture and seating; promote lifelong physical activity and use of adaptive devices to maintain mobility and independence

- Scoliosis is common, more so in adults.

RECOMMENDATIONS: Regular evaluation for scoliosis in children (especially during growth spurt) and adults; refer to orthopedics for consideration of bracing or surgery

Case Report

Recurrent fractures as a new skeletal problem in the course of Angelman syndrome

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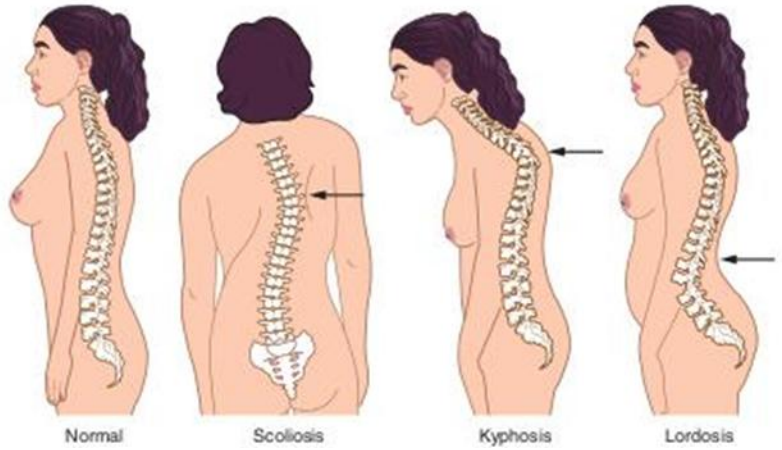
ABSTRACT

Angelman syndrome is a genetically inherited syndrome with severe retardation of psychomotor development and speech disturbances, usually accompanied by epilepsy, typical dysmorphic features, and some skeletal symptoms. The aim of the current report is to present new skeletal symptoms which may occur in the course of AS, based on a case report of an 8-year-old girl with confirmed 15q11;12 microdeletion and recurrent low-trauma bone fractures. According to our knowledge it is the first report of such skeletal symptoms in patient with a diagnosis of AS.



ELSEVIER

Bone Mineral Density in Angelman Syndrome

Giangennaro Coppola, MD*†, Alberto Verrotti, MD*†, Ciro Mainolfi, MD*‡, Gianfranca Auricchio, MD*, Delia Fortunato, MD*, Francesca Felicia Operto, MD*, and Antonio Pascotto, MD*

Our aim was to evaluate bone mineral densitometry in patients with Angelman syndrome with or without antiepileptic therapy. Eighteen patients (9 females, 9 males), aged 4.0-24.3 years (mean age, 10.1 years), and two control groups consisting of 18 epileptic and 24 healthy patients, underwent dual-energy x-ray absorptiometry at the lumbar spine (L_1-L_4), and *z* score was evaluated for each patient; the *t* score was considered for patients aged ≥18 years. Abnormal bone mineral density was present in 8/18 (44.5%) of patients with Angelman syndrome, in 7/18 (38.9%) of the epileptic group, and in none of the healthy controls. Furthermore, a significant difference regarding mean age of patients (6 versus 15 years, $P = 0.008$, by Fisher exact test), and mean length of drug treatment (3.5 versus 11.1 years, $P = 0.005$ by Fisher exact test), appeared in the group with Angelman syndrome. Most of these patients (94.4%) were receiving antiepileptic drugs, mainly valproic acid, for many years. In conclusion, our study revealed osteopenia in almost half the children and young patients with Angelman syndrome. Dual-energy x-ray absorptiometry should be performed in all patients with Angelman syndrome, particularly if they are treated with antiepileptic drugs.

Coppola G, Verrotti A, Mainolfi C, Auricchio G, Fortunato D, Operto FF, Pascotto A. Bone mineral density in Angelman syndrome. Pediatr Neurol 2007;37:411-416.

speech, gait ataxia with tremulous movements, and behavioral abnormalities including excessive laughter and apparent happiness, combined with hyperactivity. Peculiar electroencephalogram patterns, microcephaly, and epileptic seizures requiring anticonvulsant treatment are also present in 80% of patients with Angelman syndrome.

It is well-known that antiepileptic drugs are associated with osteopathy, with such manifestations as decreased bone mineral density, increased risk of fractures, and overt osteomalacia [2,3]. Osteopathy occurs not only in institutionalized patients, but also in ambulatory subjects [4].

Although the effects of valproic acid on bone density have received some attention [5-7], no such effects have been described in patients with Angelman syndrome. The aim of the present study was to evaluate bone mineral densitometry in patients with Angelman syndrome who are receiving anticonvulsant treatment, compared with epileptic and healthy control subjects.

Materials and Methods

Patients were enrolled from those followed in our clinic or recruited by the Italian Family Association of Angelman syndrome. Clinical diagnoses were performed according to recent consensus criteria [8]. Criteria for participation included: (1) age ≥3 years; (2) a molecular diagnosis of Angelman syndrome; and (3) informed consent from parents or caregivers. The study was conducted after receiving approval from the Ethics Committee of the Medical Faculty of Second University of Naples, Italy.

Exclusion criteria were: (1) hepatic or renal disorders, endocrinologic diseases, or malabsorption; (2) a familial history of abnormalities of bone metabolism or bone fractures; and (3) chronic treatment with drugs other

Gastrointestinal

- Feeding problems associated with sucking (infants due to hypotonia); swallowing issues

RECOMMENDATIONS: Evaluate feeding problems and monitor weight gain carefully. Refer for feeding and nutritional management if underweight. Occupational therapy input may help to improve fine motor and oral motor control.

Gastrointestinal (contined)

- Constipation (often due to reduced fluid intake) and GERD are common and cause pain and discomfort

RECOMMENDATIONS: Ensure adequate fluid and fiber intake; consider management strategies (especially PEG 3350) as an effective and well-tolerated medication choice for constipation; evaluate and treat GERD

- Obesity may occur (typical onset in adolescence) due to overeating and lack of exercise *(and some medications).* Possible limited sense of fullness.

RECOMMENDATIONS: Referral to dietician if overweight; *increase activity levels; control access to food if needed; use non-food rewards*

Toileting

- *Daytime bladder incontinence is common, more so in younger children and those with seizures. Incontinence can lead to physical discomfort, UTIs, dependence on caregivers and expense. Hesitancy, straining and interrupted stream have been found. Bladder may not be emptied entirely. Constipation may occur and be associated with mobility impairment, side effects of anti-convulsant medication.*

Toileting (continued)

<u>RECOMMENDATIONS</u>: Toilet training programs can help with urinary continence and reduce accidents. Relaxed state on the toilet may make voiding easier. For constipation, increase exercise, fibre and fluid; upright position on toilet, establish consistent habit time when defecation is likely. Track frequency, size and consistency of bowel movements if needed.

Head

- *Consider the possibility of headaches in relation to behavior changes, signs of pain/discomfort.*

RECOMMENDATIONS: Document possible episodes of headache (along with triggers/circumstances such as time of year, weather conditions, diet, sleep, seizure activity) and consult with health care provider

Eyes

Strabismus and refractive errors are common.

RECOMMENDATION: Opthalmology assessment when first diagnosed with AS; every 2 years afterward.

Keratoconus can occur in adults and lead to visual distortion. Can be associated with frequent eye rubbing.

RECOMMENDATIONS: Investigate cause for eye rubbing. Consider behaviour therapy to discourage eye rubbing if concern about damage to eyes.

Eyes

Ophthalmic findings in Angelman syndrome

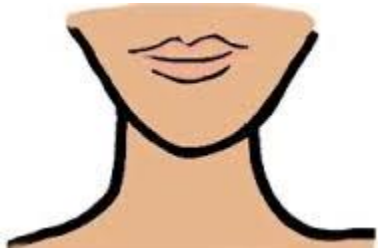
Paola Michieletto, MD,[a] Paolo Bonanni, MD,[a] and Stefano Pensiero, MD[b]

PURPOSE To provide detailed information about opthalmological findings in a group of patients with Angelman syndrome (AS).

METHODS Consecutive patients with a genetically confirmed diagnosis of AS were submitted to ophthalmic and orthoptic examinations. Strabismus, visual acuity, cycloplegic refraction, and iris and fundus pigmentation were evaluated. Parents were also examined to compare the extent of fundus pigmentation.

RESULTS A total of 34 patients were identified, representing 3 genetic classes: deletion, uniparental disomy, and mutation. Ametropia >1 D was present in 97% of cases: myopia in 9%, hyperopia in 76%, and astigmatism in 94%. Myopia and anisometropia were found only in the genetic deletion group. Strabismus, most frequently exotropia, was found in 24 patients (75%). Ocular hypopigmentation was observed in 18 subjects (53%), with choroidal involvement in 3 cases and isolated iris involvement in 4. Hypopigmentation was observed in all of the 3 genetic classes.

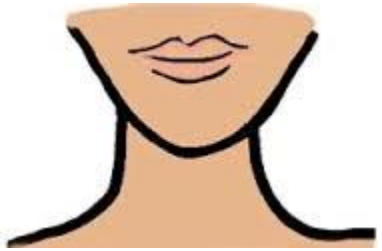
CONCLUSIONS Ophthalmic alterations in AS were observed more frequently than has been previously reported, except for ocular hypopigmentation, which was observed less frequently. (J AAPOS 2011;15: 158-161)



Ears and Throat

- High rates of swallowing/choking/aspiration are possible, associated with eating. Gagging may occur that is unrelated to eating.

RECOMMENDATION: Consider referral for swallowing study. If not possible, alert caregivers about possible occurrence of pneumonia due to aspiration risk. *Give smaller amounts/softer foods; encourage slower eating and swallowing before next bite of food; investigate sensory link to gagging.*



Ears and Throat (continued)

- Otitis media can be common in young children and show up as head banging or other self-injurious behaviour.

RECOMMENDATION: Have doctor screen for otitis media, especially in childhood and when self-injurious behaviour starts. *Signs of possible hearing problems – loss of interest (e.g., music); not responding to environmental sounds (e.g., tv turned on; refrigerator opened)*

Dental/Mouth

- Dental-related problems are possible (teeth and gum problems, teeth grinding). Other problems – excessive mouthing and chewing (possibly associated with reflux), drooling, *fingers in mouth.*

RECOMMENDATIONS: Maintain good oral hygiene and regular preventative dental evaluations. Carefully administered medications and surgical intervention for drooling may be considered. *Consider link to reflux. Teach tolerance of tooth brushing and encourage participation in oral hygiene routines. Teach child/adult to wipe mouth when drooling. Changes in chewing habits could be a sign of dental problems. Provide safe chewing objects (e.g., chewelry)*

Endocrine & Sexuality

- Puberty and development of secondary sexual characteristics are normal but may be delayed from 1-3 years

RECOMMENDATIONS: Ascertain status and discuss menstrual management. *Look for behavior changes around time of menses (mood, signs of pain)*

- Males and females are presumed to be fertile. Women are vulnerable to sexual abuse, STI, unwanted pregnancy. Masturbation possible in both genders.

RECOMMENDATIONS: Contraception may be requested to avoid unwanted pregnancy (but could increase potential for sexual abuse), *reduce menstrual flow and cramps*. *Talk to agencies about abuse policies, staff training and supervision.* Behavior therapy to teach private versus public behavior for masturbation.