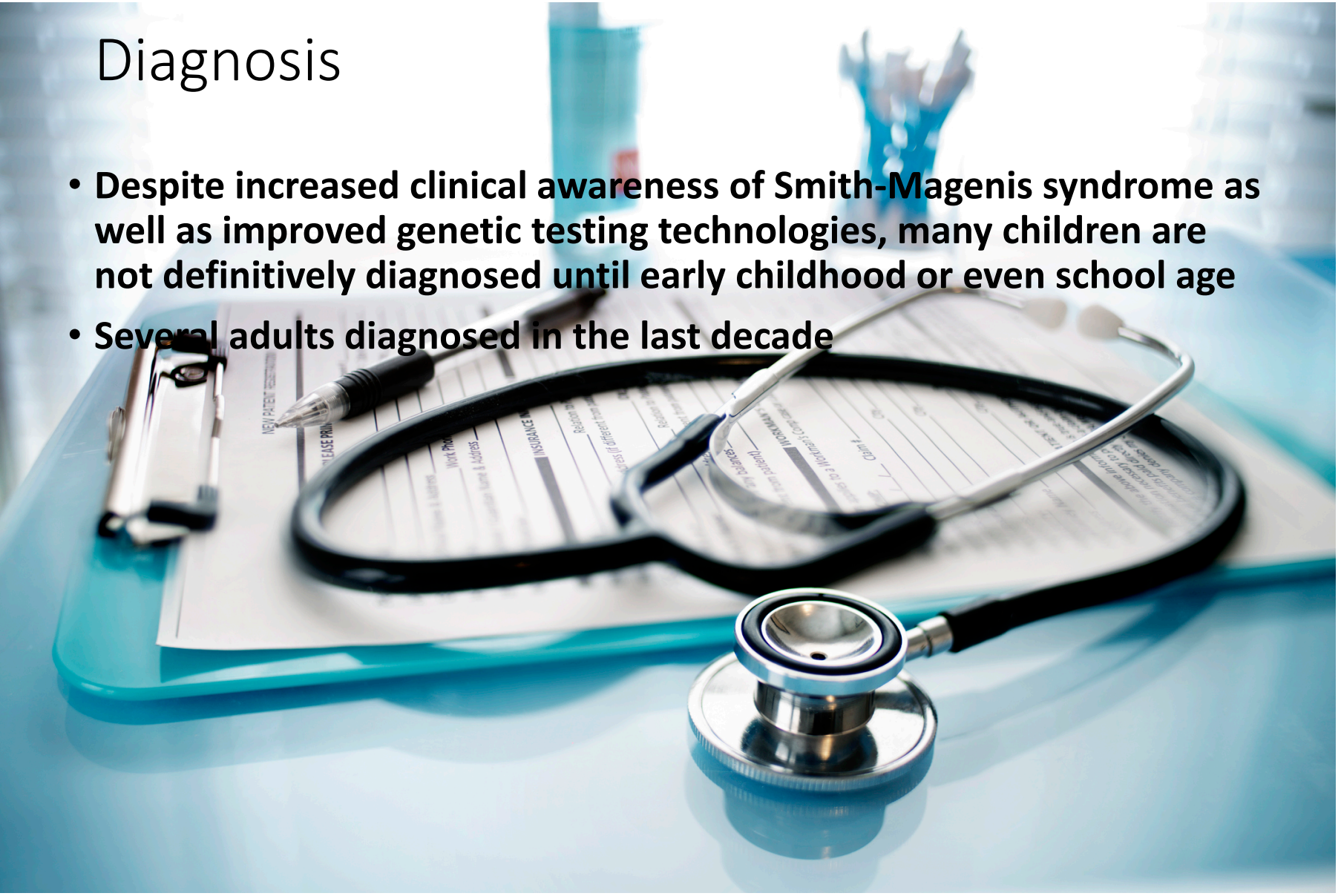
Demystifying neurological symptoms in SMS

Andrea Gropman, M.D.

Smith Magenis syndrome

- The Smith-Magenis syndrome is a rare, complex multisystemic disorder featuring, mental retardation and multiple congenital anomalies caused by a heterozygous interstitial deletion of chromosome 17p11.2 or a mutation in the *RAI1* gene

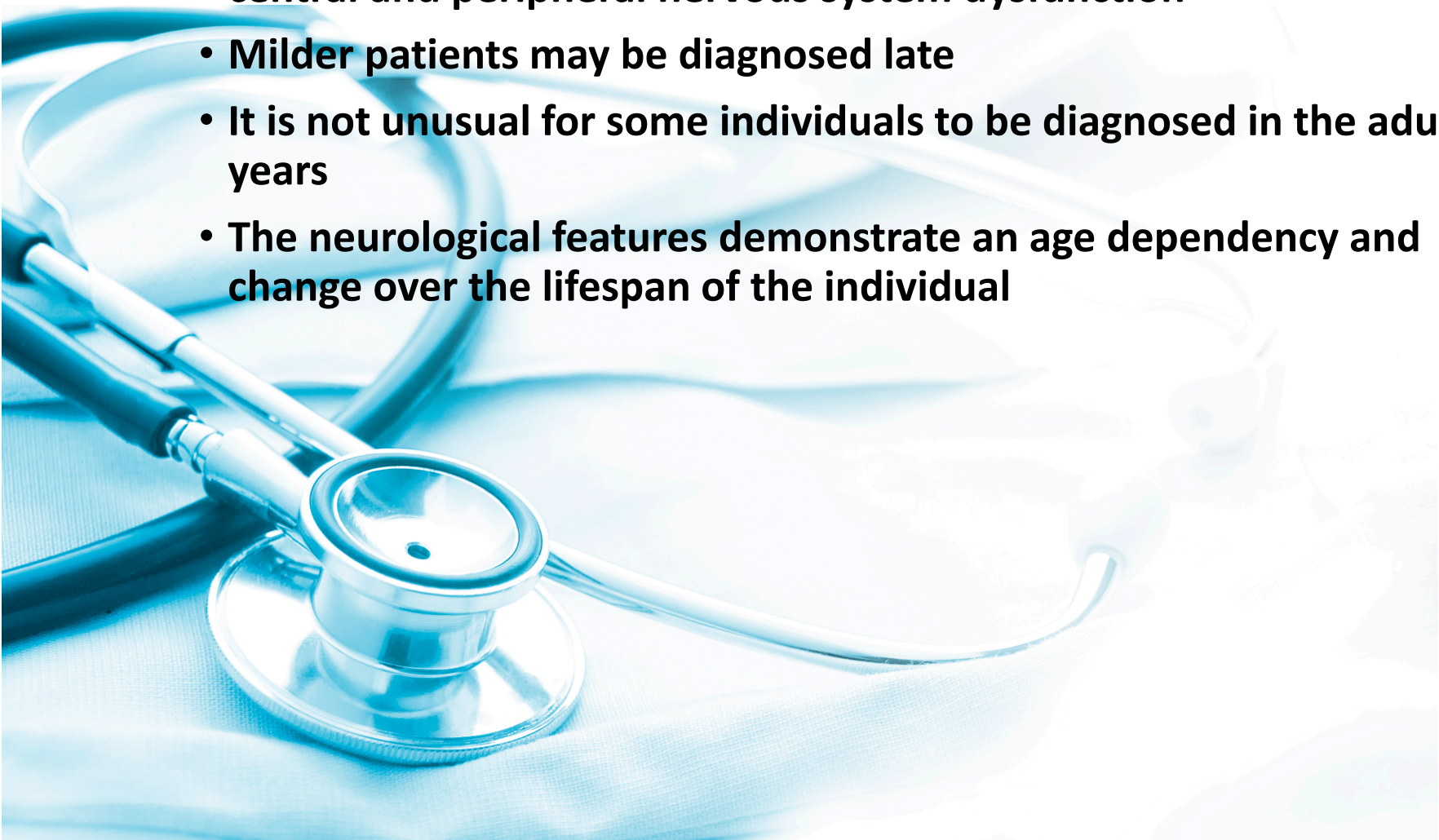
Diagnosis



- **Despite increased clinical awareness of Smith-Magenis syndrome as well as improved genetic testing technologies, many children are not definitively diagnosed until early childhood or even school age**
- **Several adults diagnosed in the last decade**

Smith Magenis Syndrome

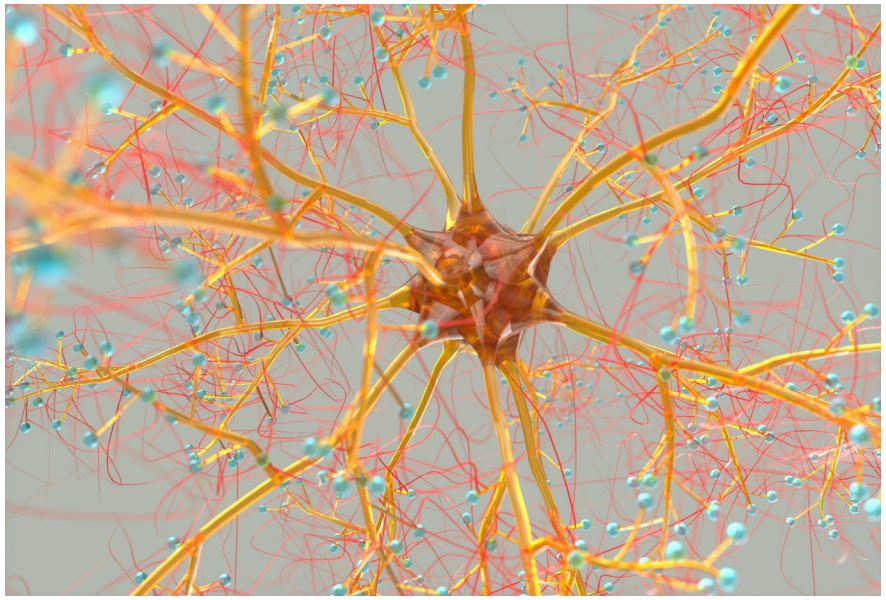
- **Individuals with Smith-Magenis syndrome present features of both central and peripheral nervous system dysfunction**
- **Milder patients may be diagnosed late**
- **It is not unusual for some individuals to be diagnosed in the adult years**
- **The neurological features demonstrate an age dependency and change over the lifespan of the individual**

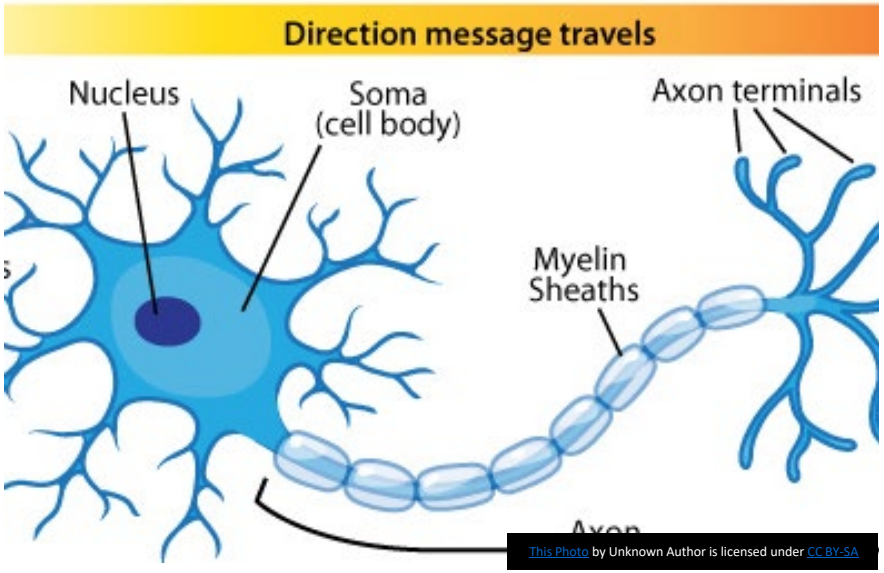


Demystifying neurological symptoms

What is the function of the nervous system?

- **To control all motor, sensory, and autonomic functions in the body**
- **We talk about the nervous system as being divided into two parts**
- **Central nervous system**
  - **Brain**
  - **Spinal cord**
- **Peripheral nervous system**
  - **Cranial nerves**
  - **Autonomic nervous system: fight or flight**
  - **Muscle**
  - **Other nerves to the muscles and organs**
  - **Junction between nerve and muscle (neuromuscular junction)**

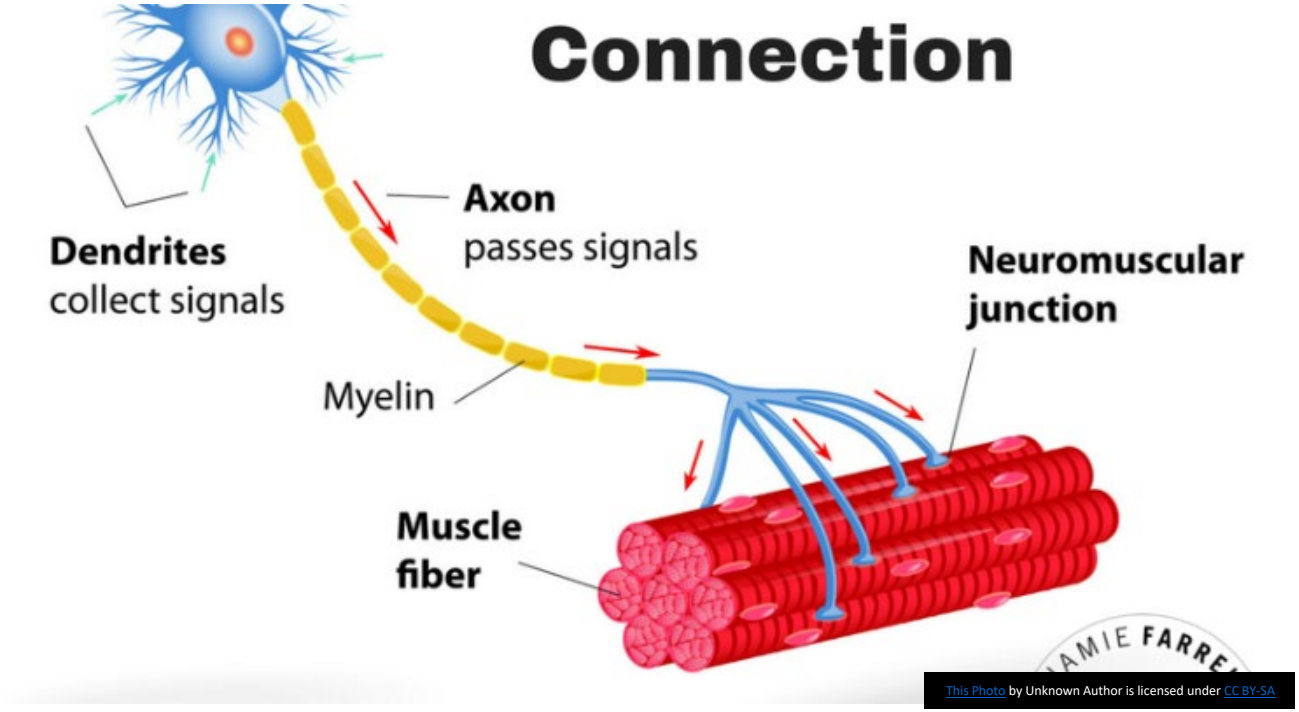




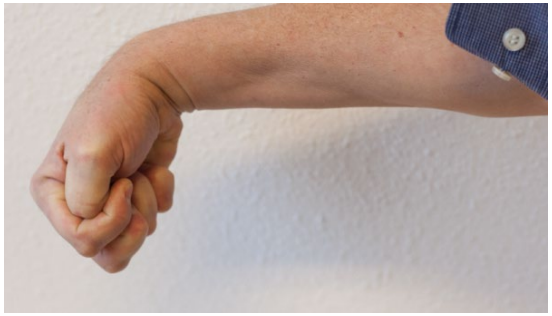
What makes up brain functional units

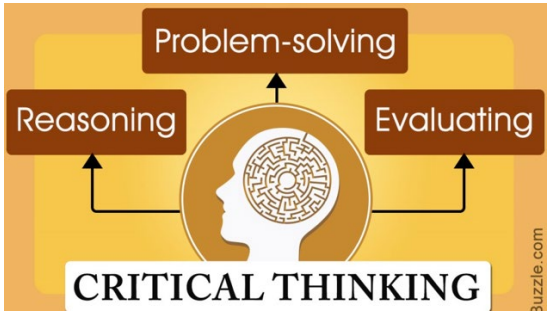
- **Neuron**
- **Axon**
- **dendrite**

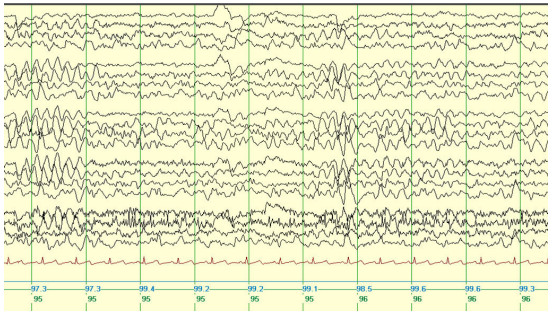
What makes up the muscle units



What symptoms come from brain and spinal cord?



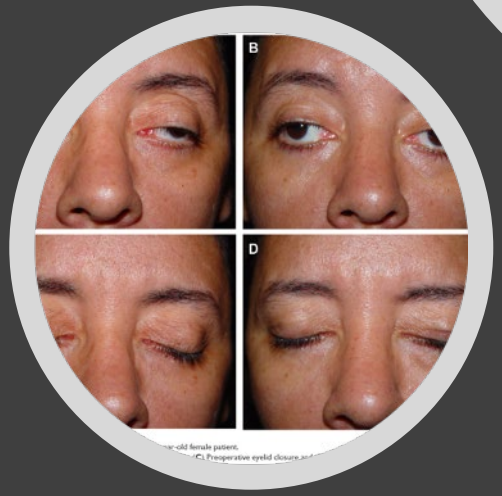




- Brain
  - Seizures
  - Low tone (hypotonia)
  - Thinking, concentration, memory problems
  - Speech
  - spasticity

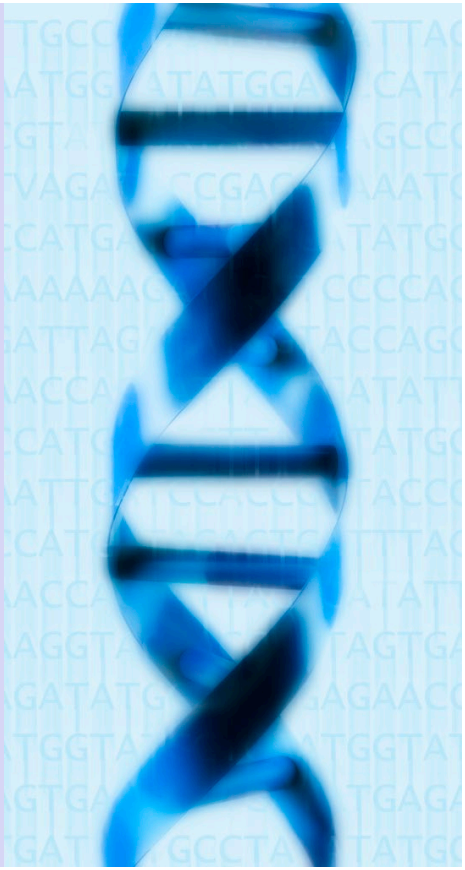
What problems come from muscle unit

- Muscle weakness
- Droopy lids (ptosis)
- Neuropathy
- Myopathic face (weak face)



SMS phenotype

- The phenotype of SMS becomes more pronounced and recognizable with advancing age
  - Physical characteristics
  - Neurobehavioral features

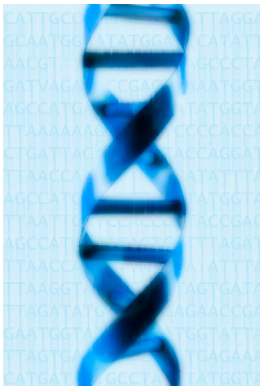


SMS phenotype

- Neurological
  - Infantile hypotonia (central)
  - Depressed DTRs, reduced pain
  - Seizures in ¼ (catamenial in many)
- Cognitive
  - significant expressive language delay
  - mental retardation
  - Behavioral problems, including self injury,
  - tantrums, and stereotypies
  - Other Neurobehavioral problems

Infants with SMs

- Present with hypotonia and gross motor delay
- Weak cry
- Decreased vocalization and complacency
- Gross and fine motor skills are delayed in the first year of life
- sensory integration
- Crying is infrequent and often hoarse in quality



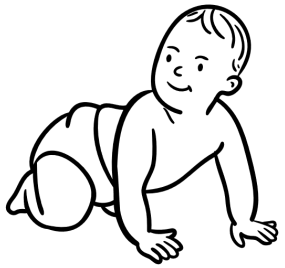


Table 3. Characteristics of the infant phenotype of Smith-Magenis syndrome

Decreased fetal movement by history	9/19
Hypotonia	19/19
Hyporeflexia	17/19
Increased daytime sleepiness and napping; perceived to be "good sleepers"	19/19
Oromotor dysfunction	19/19
Delayed gross motor skills (2–24 months behind)	19/19
Delayed fine motor skills	19/19
Marked speech delay (Expressive language <Receptive language)	19/19
Near or age-appropriate social skills	16/19
Major behavioral problems documented in first 18 mo (Average age onset of behavioral abnormalities 18–24 mo)	0/19
Sleep disorder	19/19
Cherubic facial appearance that is perceived as dysmorphic	19/19

Children with SMS

- Presentation: developmental delay, in particular expressive language delays
- Emerging neurobehavioral difficulties
- Sleep disturbance
- Differential diagnosis
  - Autism
  - Prader-Willi syndrome
  - Down syndrome
  - Velocardiofacial syndrome
  - Fragile X
  - Angelman syndrome

Neurobehavioral phenotype of SMS

- A striking neurobehavioral pattern
  - Stereotypies
  - Hyperactivity
  - Polyembolokoilamania
  - Onychotillomania
  - maladaptive
  - self-injurious and aggressive behavior is observed in SMS with increasing age

Neurodevelopmental

•Feeding difficulties (major oral sensorimotor
•dysfunction
•Failure to thrive
•Generalized hypotonia
•Alert and responsive
•Hypotonia (low muscle tone)
•Hyporeflexia
•Social skills—age-appropriate
•Delayed gross/fine motor skills

Behavior

•Diminished vocalizations and crying
•"Quiet good babies"
•Complacent
•Parent perception of "good sleeper"
•Decreased total sleep for age
•Lethargic

Neurodevelopmental

•Developmental delaysGross/fine
•motor delays
•Marked speech delay (expressive
•receptive)
•Decreased pain sensitivity
•Pes planus (flat) or pes cavus
•(high arch)
•Delayed potty training
•Sensory Integration issues

Behavior

•Stereotypic behaviors: self-hugging
•lick and flip behaviors
Self-abusive behaviors head banging;
•hitting: self wrist bitting; skin
•Picking Sleep disturbance: short sleep cycle; early risers (5:30–6:30 am);
•frequent night awakenings
•and daytime naps
•Engaging personality

•Cognitive delays
•weaknesses: sequential processing and short-term memory
•strengths: long-term memory and
•perceptual closure
•Visual learners, Pes planus or pes cavus, Bedwetting, sensory integration issues

•Attention-seeking behaviors
•Frequent outbursts/tantrums
•Sudden mood shifts
•Impulsivity/aggression
•Attention deficits
•Chronic sleep disturbance:
•short sleep cycle;
•early risers (4:30–6:30 am);
•frequent night awakenings
•and daytime sleepiness
•Stereotypic behaviors Self-injuriousbehaviors: Hitting self, nail biting or
•pulling; object insertion (older ages)Very communicative
•Excellent long-term memory

Cognitive delays
•Excellent long-term memory
•Reports of exercise intolerance
•Poor adaptive function

•Chronic sleep disturbance; decreased total sleep time; increased naps with age* (parental reports)
•Major behavioral outbursts or rage behaviors, property destruction, attention seeking
•Aggressive/explosive outbursts
•Impulsive, disobedient
•Mood shifts (rapid) without major Provocation Attention deficits Argumentative Self-injurious behaviors (hitting self/
•objects; nail yanking; object
•insertion) Mouthing of objects, bruxism. Lick and flip of pages in a book, Self-hug, upper body
•Spasmodic squeeze. Body rocking Spinning and twirling of objects. Very communicative
•Excellent long-term memory

Presentation of the clinical case

- 15 ½ year old female diagnosed at age 5 months with SMS
- She was born at term to a G1 P1 healthy mother after a brief, 2 hour labor
  - There was documented maternal beta strep infection and high fevers
- Birth weight was 6 lb 7 ounces, meconium stained
- Apgars $4^{1}8^{5}$
- She was pale at birth and fed slowly
- Medical problems have included recurrent ear infections in the first two years of life, urinary tract infections, myopia, and benign heart murmur
- She has been hospitalized for apnea, reflux and seizures

Infancy

- Typical of SMS infant
  - Weak, quiet cry
  - Swallowing and feeding coordination disorders with packing of food in mouth, choking, etc.
  - Many of them do not spontaneously awaken for feeds, sleep excessively and are lethargic and low movement

Childhood

- Difficulties with transitions of activities, changes in schedules
- Attention seeking
- Anxiety
- Hyperactivity
- Aggression towards others
- SIB
  - Hits self, bites self, hits self against objects, pulls hair, skin, or nails, grinds teeth, lick and flip of pages of book, hand/objects in mouth, hugs self and hugs others

Early development

- Early development was delayed with sitting at 12 mos (normal 9 mos); walking at 25 months (normal 12-15 mos) and language was delayed with 4-5 word sentences only emerging at 4-5 years of age

Diagnosis of SMS

- She was diagnosed with SMS at 5 months of age due to developmental delays and mildly dysmorphic features
  - Karyotype normal
  - FISH revealing deletion of 17p11.2
  - Often the diagnosis is delayed
  - In patients born prior to 1992, it has not been uncommon for early studies to be read as normal, and for repeat karyotype to be performed, finally with the 2nd or 3rd one revealing of the result

Specific SMS behaviors

- Sleep
  - The patient has had the typical sleep disorders described in the syndrome
    - Problems falling asleep
    - Problems staying asleep
    - Falling asleep in the daytime
    - Early am awakening
    - Excessive daytime sleepiness
    - Daytime sleep attacks

Specific SMS behaviors

- She suffered from oral motor and sensory integration difficulties often seen in this syndrome
- She had received supplemental services when younger-OT, PT, and speech
- Behavior has been erratic
  - Stereotypies, self hug, rage attacks
  - Medications used to try to modulate the behavior has produced side effects

Medication side effects

- Ativan worsened behavior
- Tegretol worsened behavior
- Clonidine interrupted sleep
- Imiprimine interrupted sleep
- Depakote disturbed sleep
- Cylert led to psychotic spells
- Anafranil led to sensory hallucinations
- Zarontin worsened behavior
- Keppar led to psychosis, hallucinations, SIB, violence
- Topamax led to problems with memory and coordination

Medications that have helped

- Melatonin
- Lamictal at lower dosages
- zonergran

Epilepsy

- She has epilepsy which has been seen in ¼ to 1/3 of subjects with SMS
- Three types of seizures
  - Clusters of complex partial seizures
  - Absence seizures
  - Tonic clonic seizures
- The onset of her seizure disorder has been with menarche
- She has catamenial epilepsy which is being seen with increasing frequency in our cohort of adolescent women with SMS

Physical features and exam

- Brachycephaly
- Upslanting palpebral fissures
- Small epicanthal folds
- Flat nasal bridge
- Facial dysmorphism, as infants and young children, maxillary hypoplasia, becomes relative retrognathic with age
- Triangular, down turned mouth
- Truncal and extremity hypotonia
- Extremity abnormalities
  - Fifth finger clinodactyly
  - Bridged palmar crease

Neurological features of SMS

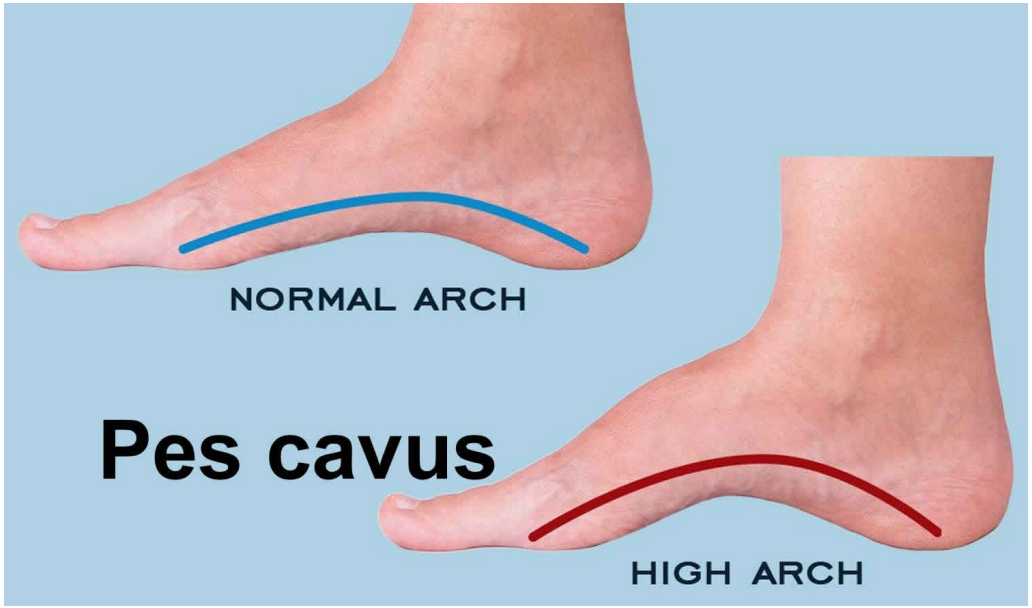
- Evidence of both central and peripheral nervous system involvement
- Central nervous system
  - Intellectual disability of variable degree
    - If more than moderate, consider comorbid condition such as HIE or other disorder
  - Speech dyspraxia
  - Central hypotonia
  - Self injurious behaviors and stereotypies
    - Specific to SMS: lick and flip and self hug
  - Sleep disorder
    - Inversion of circadian pattern of melatonin secretion results in early am awakening and sleep attacks in the daytime
    - The poor sleep may exacerbate the behavior

Neurological aspects of SMS

- Imaging studies
  - Anatomic imaging showing nonspecific ventriculomegaly
  - One autopsy case showing shortened frontal lobes
  - PET study and volumetrics show decreased activity in the insular cortex

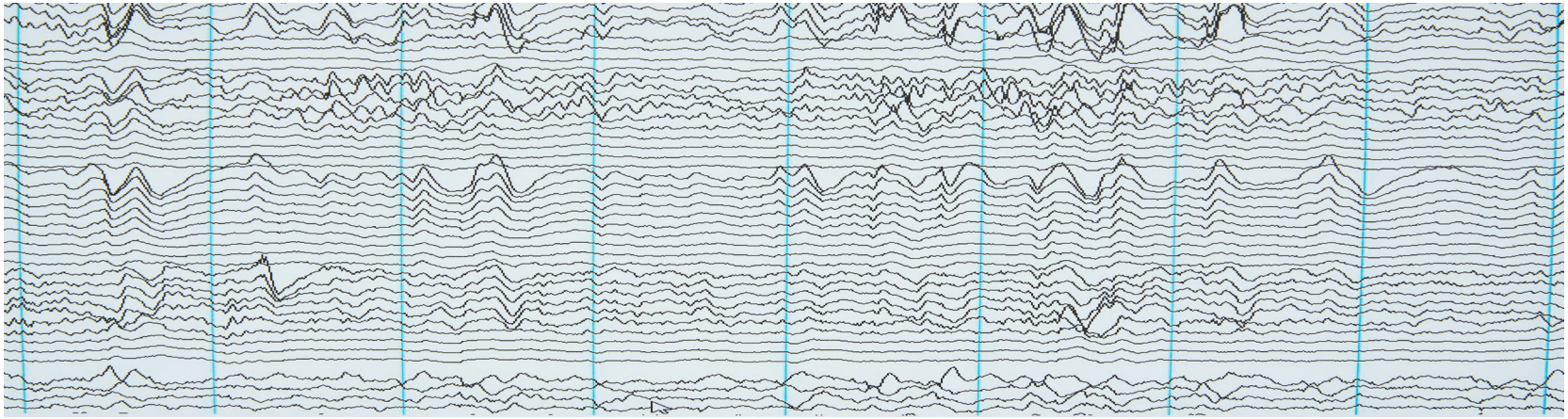
Neurological aspects of SMS

- Peripheral nervous system involvement
  - Pes cavus deformity
  - Peculiar gait
  - Apparent lack of or diminished sensation
  - Some with deletion extending into PMP22 region of 17p1.2 deletion
    - Other genes??



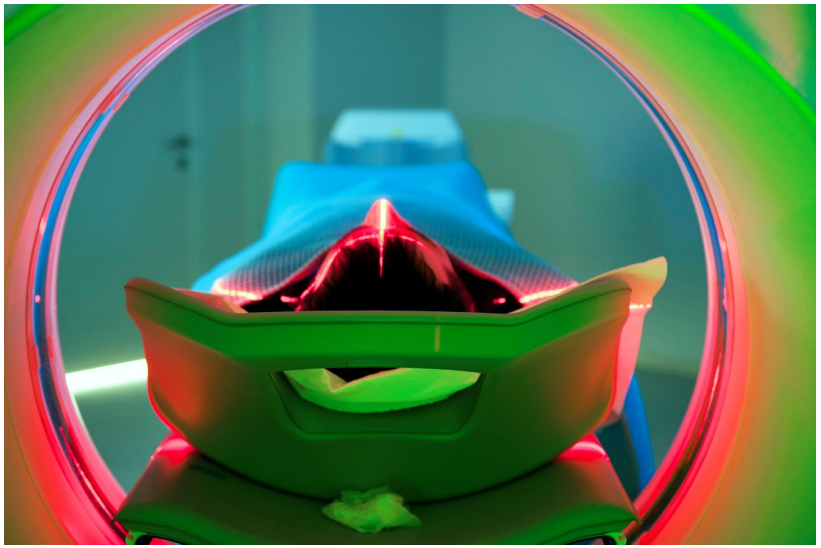
Epilepsy in SMS

- Less than ¼
- Not hard to control with anti seizure medications
- Females with seizures during menstrual cycle
- No one type is common
- Family history of seizures is a bigger risk factor than having SMS



MRI imaging in SMS

- No specific brain findings that are characteristic of SMS
- No value in MRI unless seizures or other neurological concerns
- MRI of the spine may be indicated in scoliosis



Uncharted territory

- Transitions
- Work
- Life
- Adulting
- Behavior
- Socialization