Pediatric Residents Review Session

A bit of a hodge podge to keep you guessing

December 20, 2018

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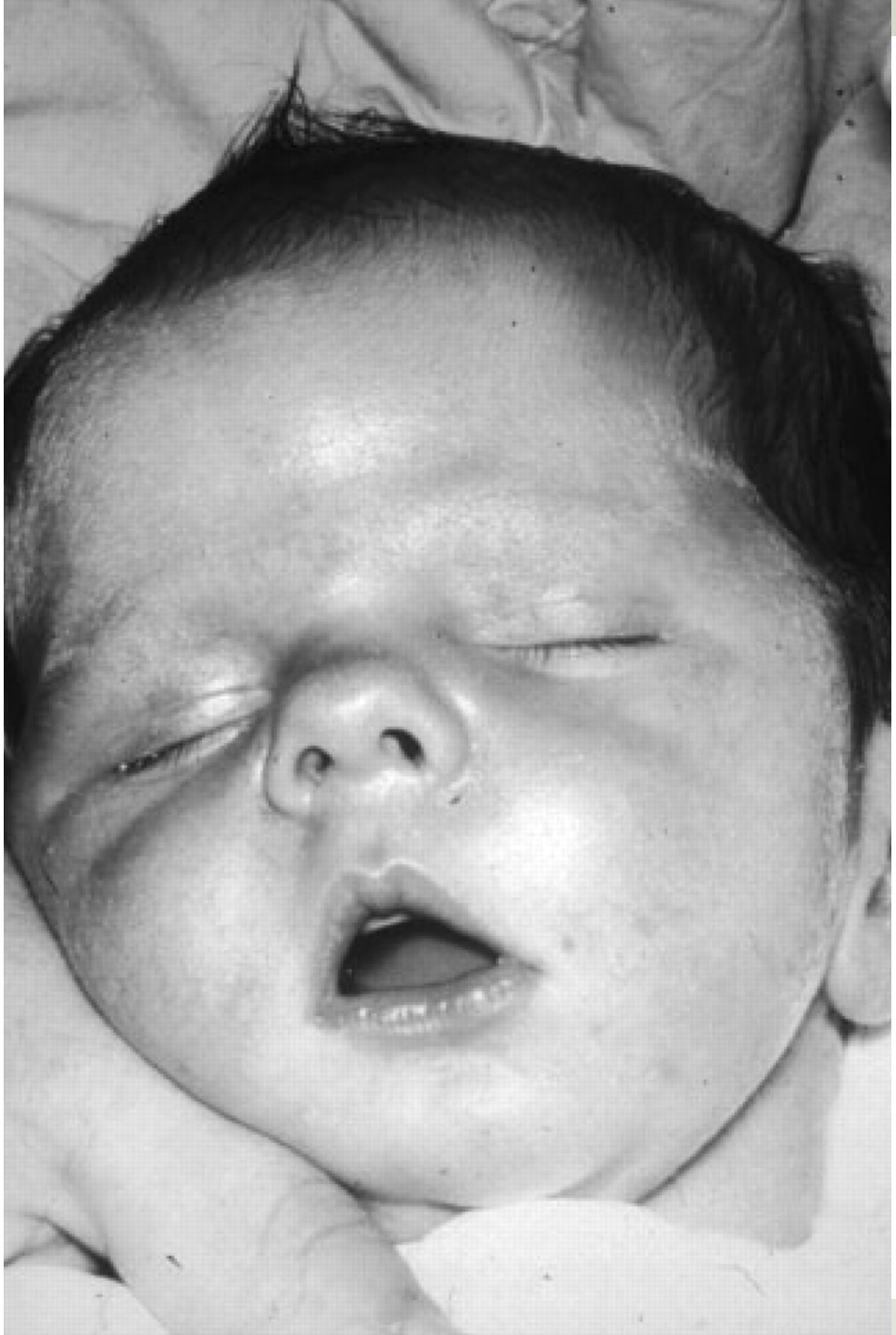
Email me for resources (OSCE handbook, etc)

Thanks to Dr. K. Smyth and Dr. K Murias for inspiration for some of the slides

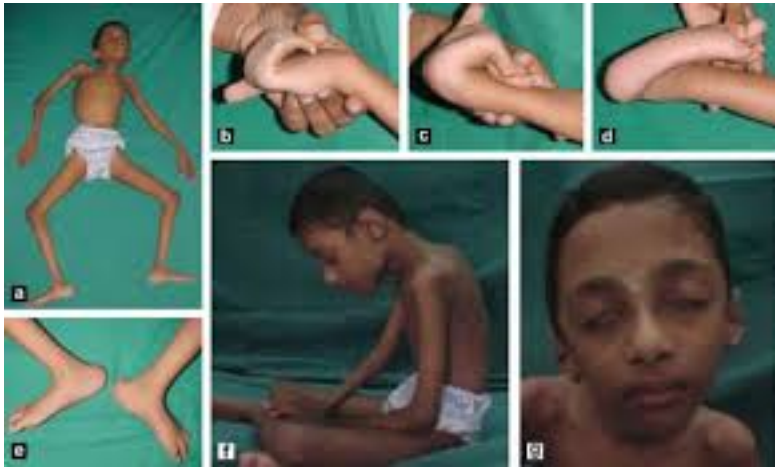
Case

- 3mo girl with hypotonia, hypotonic facies, 1+ symmetric DTR. What is the most likely diagnosis?
  a. Congenital muscular dystrophy
  b. Myotonic dystrophy
  c. SMA1
  d. Nemaline rod

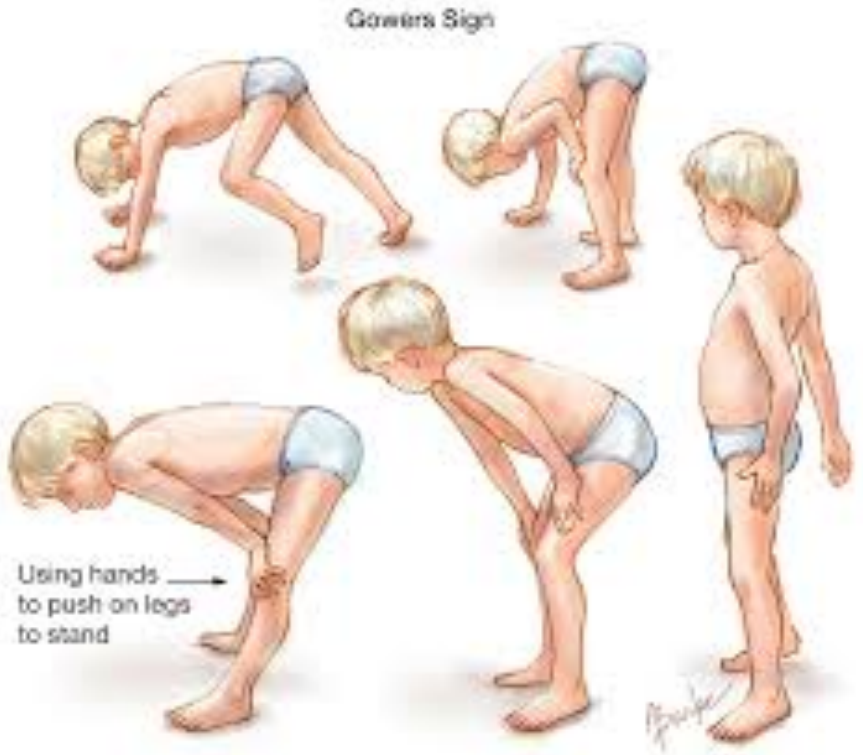


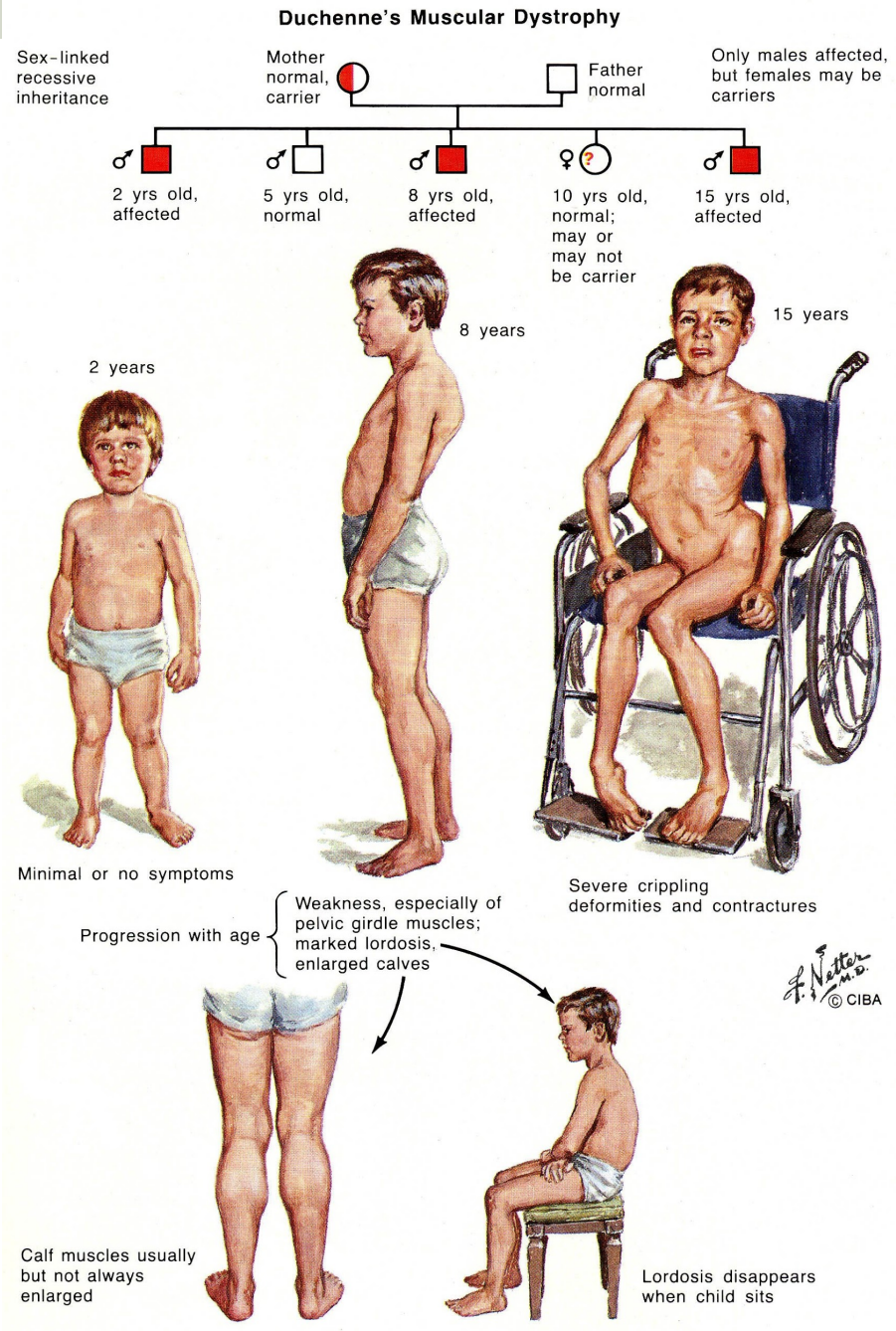
Stem not giving this picture

OR this picture



What is this?




Duchenne's Muscular Dystrophy
Sex-linked recessive inheritance
Mother normal, carrier
Father normal
Only males affected, but females may be carriers
2 yrs old, affected
5 yrs old, normal
8 yrs old, affected
10 yrs old, normal; may or may not be carrier
15 yrs old, affected
2 years
8 years
15 years
Minimal or no symptoms
Progression with age
Weakness, especially of pelvic girdle muscles; marked lordosis, enlarged calves
Severe crippling deformities and contractures
F. Netter M.D.
© CIBA
Calf muscles usually but not always enlarged
Lordosis disappears when child sits

Dystrophinopathies

Duchenne Muscular Dystrophy

Becker Muscular Dystrophy

Dystrophinopathies

- By convention, if boy stops walking before age 12, this is **Duchenne Muscular Dystrophy (DMD)**
- If they remain ambulatory after their 16th birthday, are typically considered to have **Becker Muscular Dystrophy (BMD)**
- **Anything in between is an <u>intermediate phenotype</u>**
- Some centres transition to using *Dystrophinopathies* as the term
- Dystrophinopathies are **X-linked** disorders

Dystrophinopathies: Epidemiology

- Duchenne Muscular Dystrophy
  - 1:3500 live male births but newborn screening places the incidence closer to 1:5000 live male births
  - Mean lifespan 19 years traditionally, now greater than 25 years (with multidisciplinary team management and corticosteroid use)
- Becker Muscular Dystrophy
  - Incidence $1/10^{th}$-$1/5^{th}$ of DMD
  - Prevalence 60-90% more than DMD

DMD: Clinical Features

- Boys often present between 3-5 years of age
  - Delayed **motor** milestones and **falls,** difficulty **running** and **jumping**
  - Gain motor milestones through 6-7 years of age, progressive weakness after
  - **Wheelchair before age 12, historically**
- Examination
  - Calf hypertrophy
  - Mild lordotic posture
  - Waddling of gait
  - Poor hip excursion during running
  - Head lag when pulled from sitting from supine
  - Partial Gower maneuver when rising from floor.

DMD: Clinical Features

- Joint contractures in ankles – **early** (while ambulating)
  - Then hips, knees, elbows, and wrists
- Kyphoscoliosis
- Pulmonary Function Declines
- Cardiac Involvement
  - Sinus Tachyardia, Atrial/Ventricular Arrythmias – Typically from **Cardiac Fibrosis** and **Dilated Cardiomyopathy**
- Cognitive involvement
  - 30% develop intellectual disability (Verbal IQ > Performance IQ)
  - ADHD (10-15%)
  - Autism Spectrum Disorder (3-6%)
  - Obsessive Compulsive Disorder (5%)
- Endocrine: Osteoporisis
- Ophthalmology: Cataracts

DMD: Treatment

- Corticosteroids
  - Prolong walking, transient increase in muscle strength, reduce falls, improve pulmonary function, decrease scoliosis, may improve cardiac and cognitive function
  - No consensus on time of treatment (5-7yrs of age vs 3-4, prior to losing milestones)
  - No optimum dosing
    - 1) prednisone 0.75mg/kg/d
    - 2) deflazacort 0.9mg/kg/d
    - 3) prednisolone 0.75mg/kg/d for 10 days, alternating
    - 4) prednisone 2.5mg/kg to 5mg/kg every Friday and Saturday
  - Receive immunizations prior, start Vitamin D and have family dietary counseling.
  - May still confer benefit after loss of ambulation

Becker Muscular Disease (BMD): Clinical Features

- Large variability in weakness
- May begin as early as 5-6 years of age or may start in 5^{th}-6^{th} decade
- **Any male patient with a limb-girdle pattern of weakness at any age should be evaluated for a dystrophinopathy irrespective of family history**

BMD: Clinical Features

- Cardiac involvement does **not** correlate with skeletal muscle disease.
  - Early referral with regular follow up from cardiologist is important.
- Pulmonary involvement typically milder than DMD
- Cognitive function is typically normal, but learning disabilities slightly more common

Dystrophinopathy gene carriers

- Young girls rarely can present with phenotype identical to DMD, usually from skewed X-Chromosome inactivation.
- CK may be elevated in 30-60% of carriers
- 40% of carriers had symptoms or signs of dystrophinopathy
  - Muscle weakness 17%
  - Dilated Cardiomyopathy 8%-14%
- **All female first degree relatives of patients with DMD or BMD should undergo DNA analysis, and if tested positive, should be evaluated for evidence of weakness or cardiac involvement**

Dystrophinopathies: Diagnosis

- Mutations in *DMD*, encoding *dystrophin*
  - Found in Skeletal, Cardiac, and Smooth Muscle Fibres, Cortical, Purkinje, Schwann, Glial, Retinal and Renal Cells.

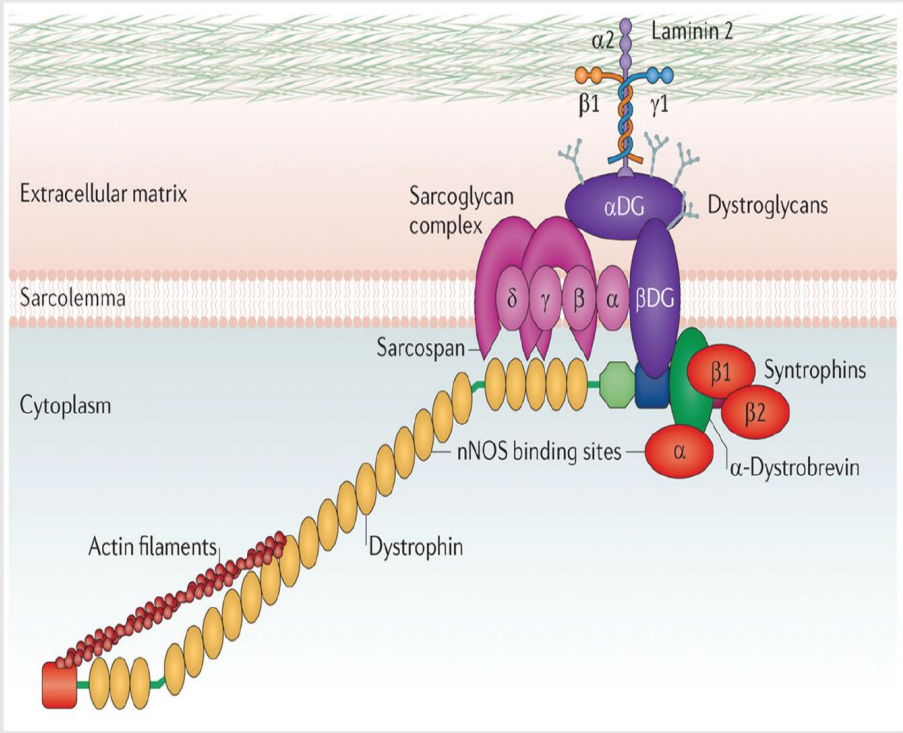


FIGURE 2-2 Dystrophin glycoprotein complex. Dystrophin, along with α-, β-, γ-, and δ-sarcoglycan, β-dystroglycan, sarcospan, syntrophins, dystrobrevin, and nitric oxide synthase form the dystrophin-glycoprotein complex.

Dystrophinopathies: Investigations

- CK
  - Elevated 10-20x (typically >3000 U/L)
- ALT, AST
  - Elevated from muscle involvement (GGT will typically be **normal**)
- DNA analysis of dystrophin gene is **first diagnostic procedure**
- EMG: myopathic motor units

Dystrophinopathies: Mutations

- Out of frame mutations (Reading frame disrupted)
  - Truncated mRNA that is rapidly degraded
  - **Absence of dystrophin in muscle □ DMD**
- In frame mututations (Reading frame is maintained)
  - Shorter and less stable dystrophin
  - More often a BMD phenotype
- 20-30% of cases, the mother does **not** test positive for the mutation
  - High rate of de-novo mutations
  - False maternity
  - Germ-line mosacism
    - **Negative testing in a mother does not preclude the possibility of an affected boy in the subsequent pregnancy**

Dystrophinopathies Mutations

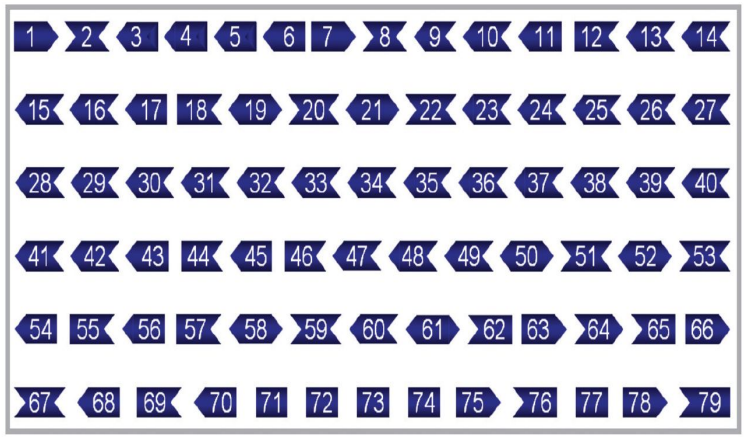


FIGURE 2-6 Reading frame rule for dystrophinopathies. Each exon must connect with the preceding and following exon, but not all exons can interact with each other. For example, deletion of exon 39 would require exon 38 and exon 40 to reconnect, and they can do so. This would lead to a slightly shorter protein of fairly good function, and the reading frame would be maintained. This would yield a Becker phenotype. However, with deletion of exon 50, exon 49 and exon 51 cannot reconnect. This leads to a dystrophin RNA transcript that stops at exon 49. These truncated RNA transcripts rapidly undergo RNA decay leading to a near total lack of dystrophin and a Duchenne phenotype. In this case, the reading frame was broken. Deletion of exons 58 to 67 in the 4-year-old boy in **Case 2-1** allows exon 57 to anneal to exon 68, retaining the reading frame. However, dystrophin's attachment site to β-dystroglycan at the sarcolemma falls within exons 58 to 67. Thus, the patient's dystrophin cannot anchor to the sarcolemma, leading to significant sheer forces and subsequent muscle fiber damage. Patients whose mutations cannot anchor to the sarcomere or the sarcolemma manifest the more severe Duchenne phenotype.

Courtesy of Annemieke Aartsma-Rus, PhD.

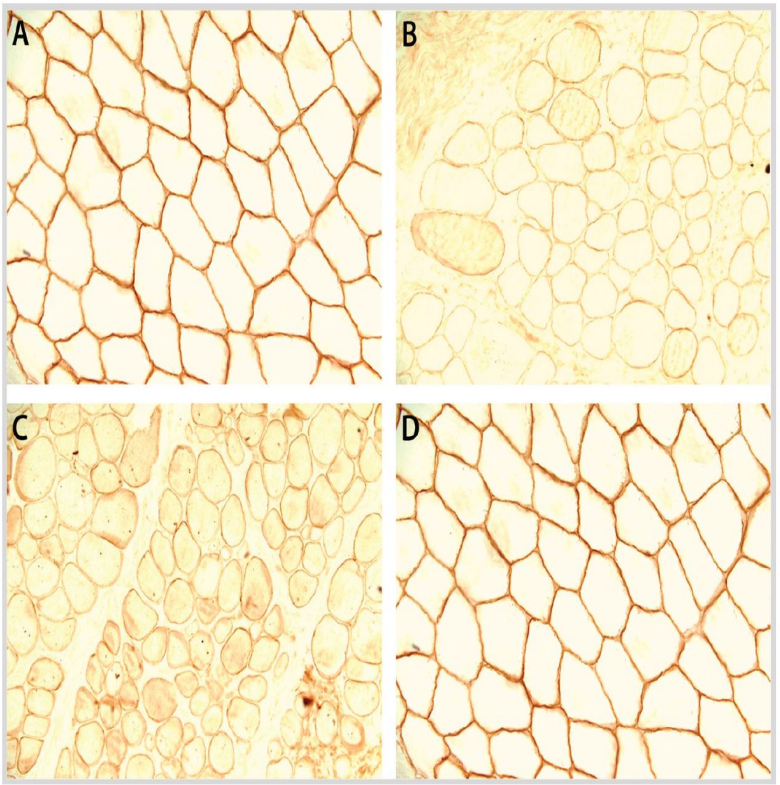


FIGURE 2-5 Dystrophin immunostaining (400X). Normal control (*A*) and decreased immunostaining to the N terminus (*B*), rod domain (*C*), and C terminus (*D*).

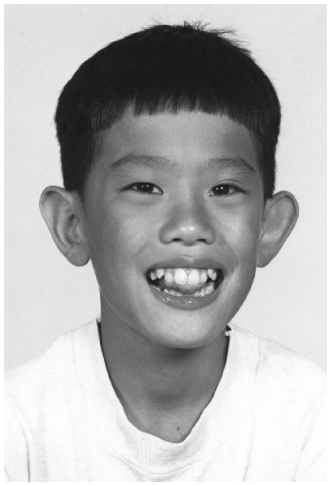
Courtesy of Charles S. Specht, MD.

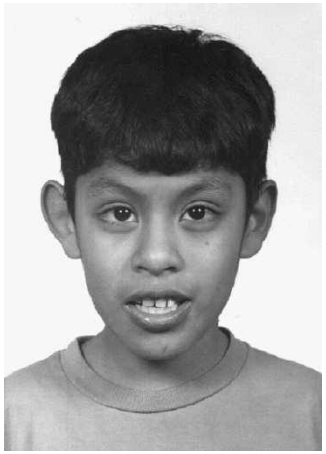
6 y.o. male with referred to your office for mild hypotonia and query autism. The patient is extremely shy and avoids eye contact and on occasion has been seen flapping his hands, however he does have 1-2 friends at school and plays well with others once comfortable doing so. He struggles at school and is being held back in grade 1 for an extra year.

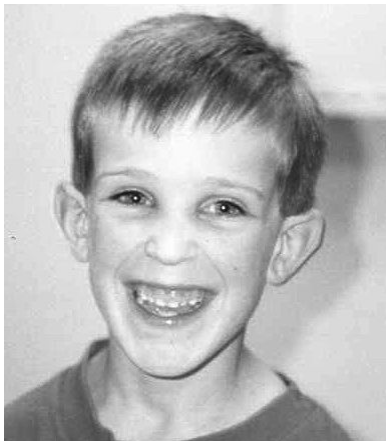
- What is the most likely diagnosis ?

- How does it manifest in females? In adults?

6 y.o. male with referred to your office for mild hypotonia and query autism. The patient is extremely shy and avoids eye contact. He struggles at school and is being held back in grade 1 for another year.

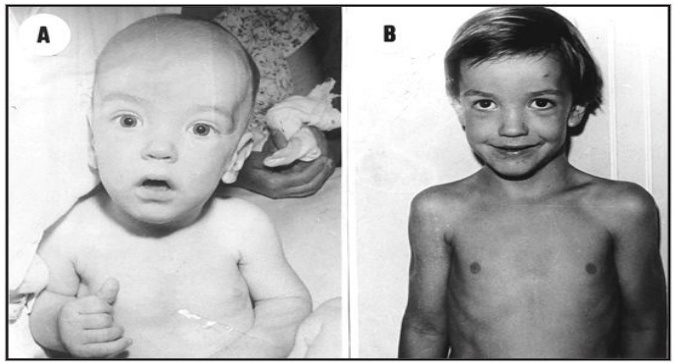


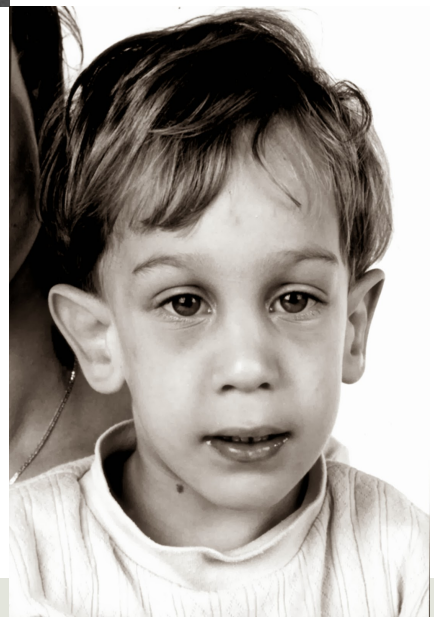


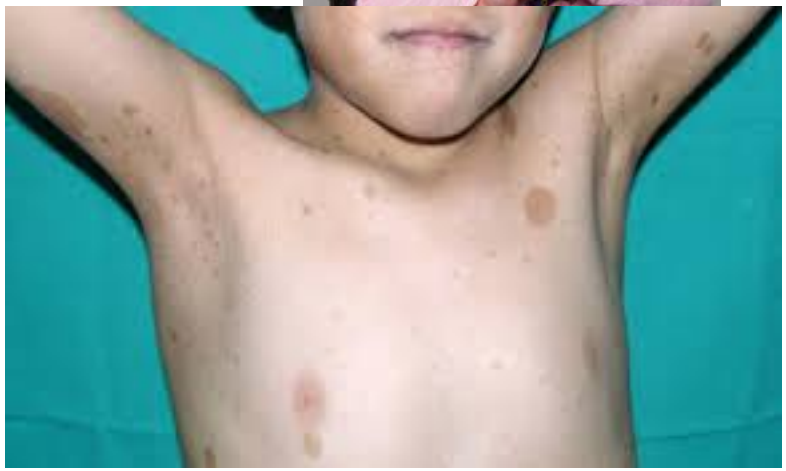


- What is the most likely diagnosis ?
  - Fragile X syndrome, FMR1 gene, CGG trinuc repeat
  - Premutation 55-200, fragile X >200
- How does it manifest in females? In adults with premutation?
  - Females: excessive shyness, primary ovarian failure esp if premutation (25%), decreased fertility, may have learning disabilities
  - ADULTs with FXTAS: tremor, ataxia, parkinsonism, progressive dementia

Name 5 genetic conditions with associated ASD (more common)

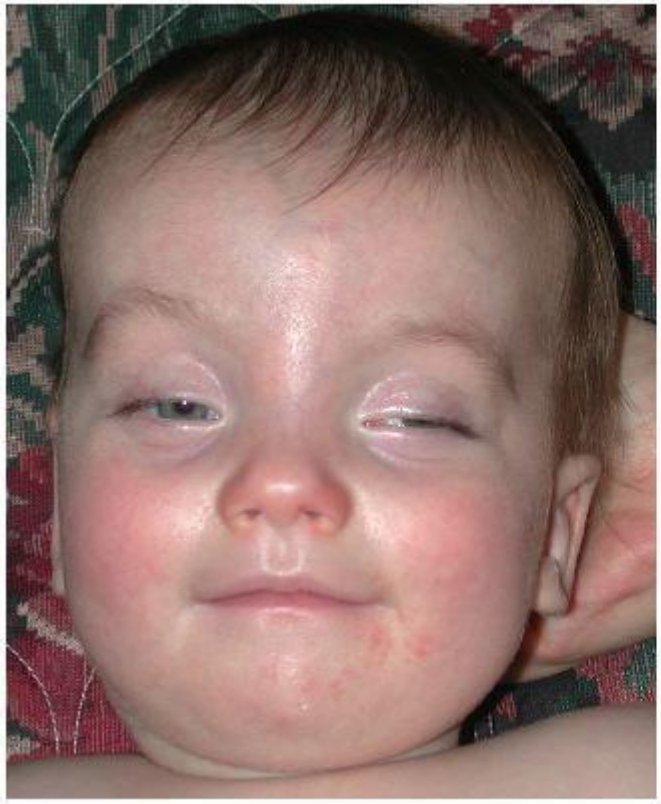


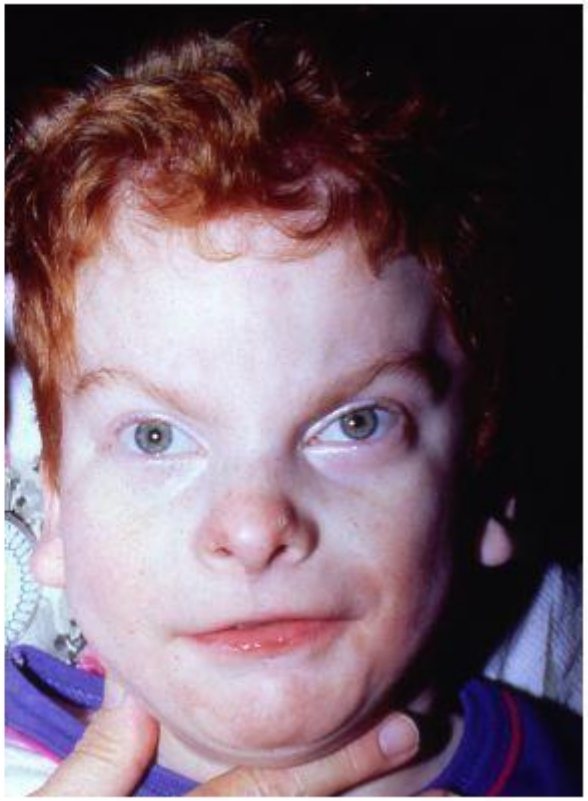


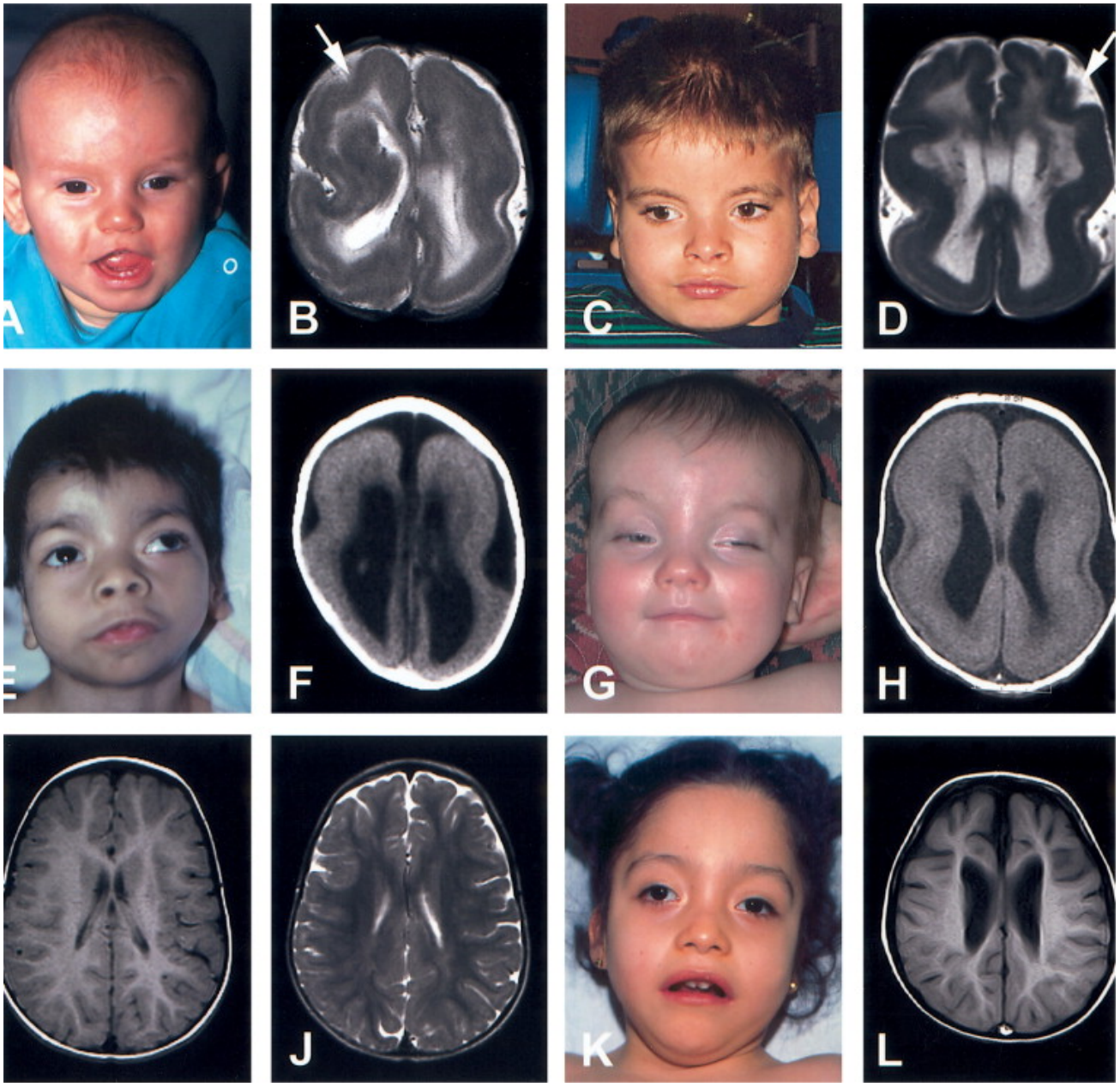


- Fragile X
  - 20-50% of boys will have ASD
- TSC
  - 25-60%
- 15q syndrome
- Rett
- 22q11 deletion syndrome
- NF1
- Smith-Lemli-Opitz
- Cerbral folate deficiency
- Biotinidase deficiency
- PKU

Name the syndrome






A
B
C
D
E
F
G
H
J
K
L

Miller Dieker

- Defect in 17p (17p13.3 deletion)
- Agyria and microcephaly
- Poor feeding
- Craniofacial defects
- Cardiac defects
- Genital abnormalities

- Case example: term infant with hypotonia, abnormal MRI

- Name 3 primitive reflexes and when they extinguish

Reflex	Age at emergence	Age at disappearance
Moro	27wks	6m
ATNR	35wks	6m
Suck, Root	2nd trimester	4m
Grasp	27wks	2m
Placing and stepping	34-37wks	1-2m
Galant	24wks	12m

Compare panioutopoulos and gastaut based on age of onset, duration of seizures, frequency of seizures and prognosis

	Paniotopoulous (Pukers)	Gastaut (Googely eyed)
Av age of onset	**3-5 years** (1-14 years) (ILAE: 3-6) Median age: 5 (2-12 yrs)	**Peak 8-9yrs** (15mo-19yrs)
Sz duration	**Prolonged** •typical sz: autonomic/behavioral disturbances, w/ vomiting, eye deviation, altered awareness. •seizures are often prolonged (often ~30 minutes; 1/3 have status)	**Brief** (seconds to < 3 minutes but rarely up to 20 minute) are often frequent ILAE: most <3 minutes
Sz frequency	**Infrequent** (1/3 have only 1 sz)	**Frequent**
Prognosis	Often sz controlled by Tx 6% ongoing infrequent seizures - no Tx was preferred for infrequent sz 6% had frequent seizures •self remitting common - sz rarely occur after 13yo •(ILAE): **resolve** by 11-13yrs	•Remission occurs in 50-60% of patients within 2-4 years after onset ILAE: remission of seizures occurs within 2-4 years from onset. •Comorbid **CSWS** in has been reported; consider sleep EEG •A dramatic response to carbamazepine is seen in more than 90% of patients
Other notes	tonic eye deviation, vomiting 2/3 **nocturnal** Rare photosensitivity occipital lobe epilepsy -PROMINENT autonomic features	Childhood occipital lobe epilepsy •visual seizures with elementary visual hallucinations occur from **awake** - have rapid onset •"fixation-off" sensitivity for giant spikes •Can have nausea and vomiting too

Name 10 causes of acquired microcephaly

- Normal HC at birth with subsequent microcephaly

Single gene defects

- Rett syndrome
- Aicardi-Goutieres
- Ataxia telangiectasia
- Cockayne syndrome
- Cohen syndrome
- X-linked lissencephaly with abnormal genitalia

Contiguous gene deletion:

- Miller Dieker syndrome

Inborn errors of metabolism

- Congenital disorders of glycosylation
- Mitochondrial disorders
- Peroxisomal disorders
- Glucose transporter defect
- Menkes
- Congenital disorders of amino acid metabolism
- Organic acidemia

- "Acquired"
  - Injuries: traumatic, HID, Ischemic stroke, hemorrhagic stroke
  - Infections: congenital HIV encephalopathy, meningitis, encephalitis
  - Toxins: lead poisoning, chronic renal failure
  - Deprivation: hypothyroidism, anemia, congenital heart disease, malnutrition

Table II: Causes of primary microcephaly: overview

1. Genetic causes

Numerical chromosomal aberrations or microdeletion and/or duplication syndromes

Trisomy 13, 18, 21 etc.

Monogenetic microcephaly

Autosomal recessive microcephaly (*MCPH1-10, MCPHA*)
Nijmegen breakage syndrome (MIM#251260)
Autosomal dominant microcephaly
X-chromosomal microcephaly
Aicardi–Goutières syndrome (MIM#225750, 610329, 610181, 610333, 612952)
Cockayne syndrome (MIM#216400, 133540, 216411)
Cornelia de Lange syndrome (MIM#122470, 610759, 614701, 300590, 300822)
Rubinstein–Taybi syndrome (MIM#180849)
Feingold syndrome (MIM#164280, 614326)
Rett syndrome, congenital (MIM#164874)
Mowat–Wilson syndrome (MIM#235730)
Smith–Lemli–Opitz syndrome (MIM#270400)
Seckel syndrome (MIM#210600, 606744, 608664, 613676, 613823, 61472)
Ligase IV syndrome (MIM #606593)
Mutations in *ATRX* gene (MIM*300032)
Mutations in *ARX* gene (MIM*300382)
Mutations in *PQBP1* gene (MIM*300463)
Mutations in *ASNS* gene (MIM*108370)
Borjeson–Forssman–Lehmann syndrome (MIM#301900)

Imprinting disorders

Angelman syndrome (MIM#105830)

2. Metabolic cause (genetic aetiology)

Serine biosynthesis disorder
Sterol biosynthesis disorder
Mitochondriopathy, e.g. pyruvate dehydrogenase deficiency
Congenital disorders of glycosylation syndrome
Rare congenital metabolic diseases (see text)

3. Exogenic factors

Intrauterine infection

Toxoplasmosis, rubella, cytomegalovirus, herpes simplex, varicella zoster virus, syphillis, human immunodeficiency virus

Teratogens

Alcohol, cocaine, antiepileptic drugs, lead/mercury intoxication, radiation

Disruptive incident

Vascular incident (stroke), intrauterine death of twin

Maternal disease

Hyperphenylalaninaemia
Maternal anorexia nervosa

Extreme insufficiency of placenta

Side effects of valproic acid

- Other than nausea, weight gain, terratogenicity, hepatotoxicity, and thrombocytopenia, name 8 side effects of VPA

- Dose related
  - Alopecia
  - Peripheral edema
  - Tremor (esp if combo w/ lamotrigine)
  - Weight gain
  - Thrombocytopenia
- Idiosyncratic
  - Pancreatitis (1:40 000)
  - Encephalopathy
  - Hepatoxocitiy (1/49 000 in pts >2 years monotherapy) or 1/7000)
  - Hyperammonemia
  - SLE
  - Fanconi syndrome
  - Terratogenicity

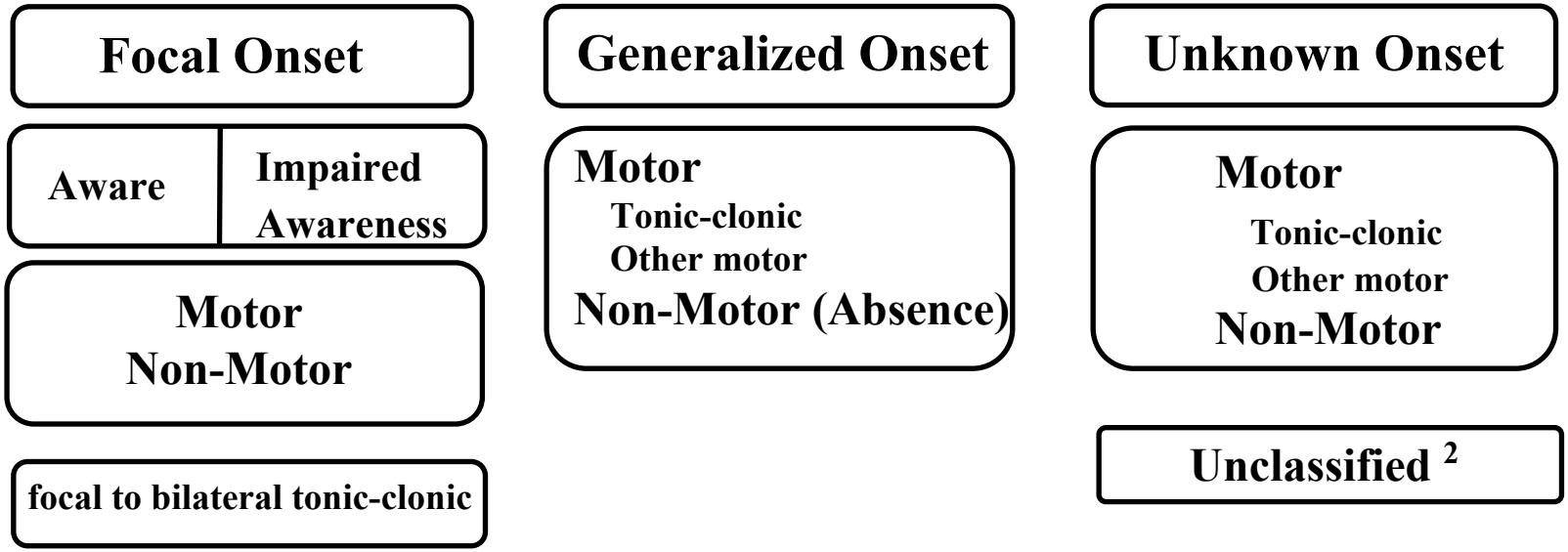
ADHD treatments

Class	Examples	Side effects
Stimulants	Dextroamphetamine Methylphenidate Modafinil	insomnia, decr appetite, weight loss, depression, psychosis, rebound phenomenon, cardiac
SNRIs Selective norepinephrine reuptake inhibitors	Atomoxetine (Strattera)	GI symptoms, weight loss, mild increase in BP/ HR,
TCAs	Amytriptyline, imipramine, clomipramine	ECG abnormalities, overdose fatal, anticholinergic effects (dry mouth, constip, blurred vision), mild increase in diastolic BP
Antidepressants	Fluoxetine, citalopram, sertraline Buproprion, venlafaxine	irritability, insomnia
Alpha2-agonists	Clonidine, Guanfacine	sedation, hypotension, dry mouth

In a patient with febrile seizures, name 4 risk factors for febrile seizures and 4 for future risk of epilepsy

Febrile Seizure Risk Factor	Epilepsy Risk Factor
Family history of febrile seizures	Family history of epilepsy
<18 months of age	Abnormal neurodevelopment
Low peak temp	Complex febrile seizure
Short duration between fever and seizure	Short duration between fever and seizure

ILAE 2017 Classification of Seizure Types Basic Version [1]



[1] Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

[2] Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

ILAE 2017 Classification of Seizure Types Expanded Version[1]

Focal Onset

Aware	Impaired Awareness

Motor Onset
- automatisms
- atonic[2]
- clonic
- epileptic spasms[2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms[2]

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified[3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.

2 These could be focal or generalized, with or without alteration of awareness

3 Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

Key Seizure Signs and Symptoms?

Symptoms	Medical Term
automatic behaviors	automatisms
emotions or appearance of emotions	emotions
extension or flexion postures	tonic
flushing/sweating/piloerection	autonomic
jerking arrhythmically	myoclonus
jerking rhythmically	clonus
language or thinking problems, deja vu	cognitive
lid jerks	eyelid myoclonia
limp	atonic
numb/tingling, sounds, smells, tastes visions, vertigo	sensations
pausing, freezing, activity arrest	behavior arrest
thrashing/pedaling	hyperkinetic
trunk flexion	spasm

Rules for Classifying Seizures (1 of 2)

Onset: Decide whether seizure onset is focal or generalized, using an 80% confidence level.

Awareness: For focal seizures, decide whether to classify by degree of awareness or to omit awareness as a classifier.

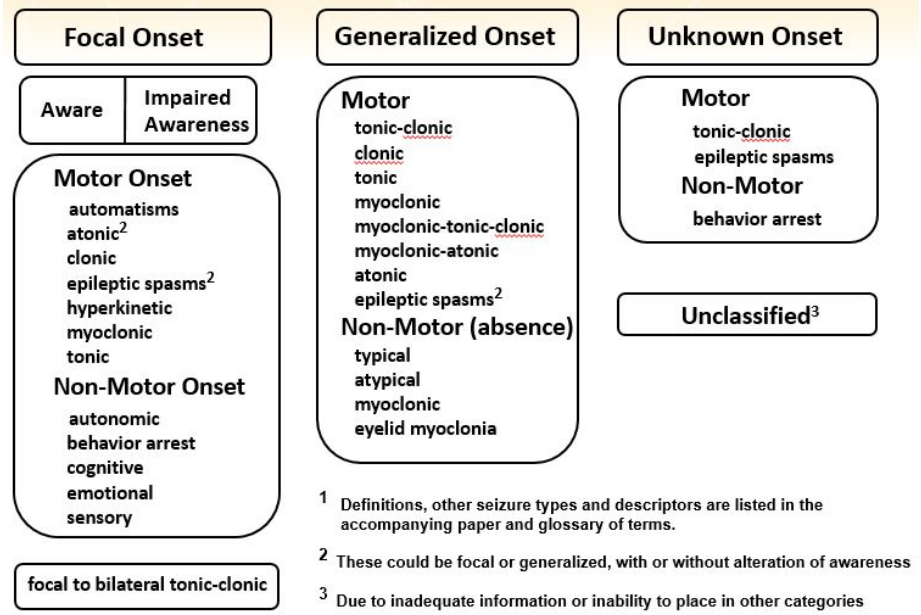
Impaired awareness at any point: A focal seizure is a *focal impaired awareness seizure* if awareness is impaired at any point during the seizure.

Onset predominates: Classify a focal seizure by its first prominent sign or symptom. Do not count transient behavior arrest.

Behavior arrest: A *focal behavior arrest seizure* shows arrest of behavior as the prominent feature of the entire seizure.

Motor/Non-motor: A *focal aware or impaired awareness seizure* maybe further sub-classified by motor or non-motor characteristics. Alternatively, a focal seizure can be characterized by motor or non-motor characteristics, without specifying level of awareness. Example, a *focal tonic seizure*.

Rules for Classifying Seizures (2 of 2)



Optional terms: Terms such as motor or non-motor may be omitted when the seizure type is otherwise unambiguous.

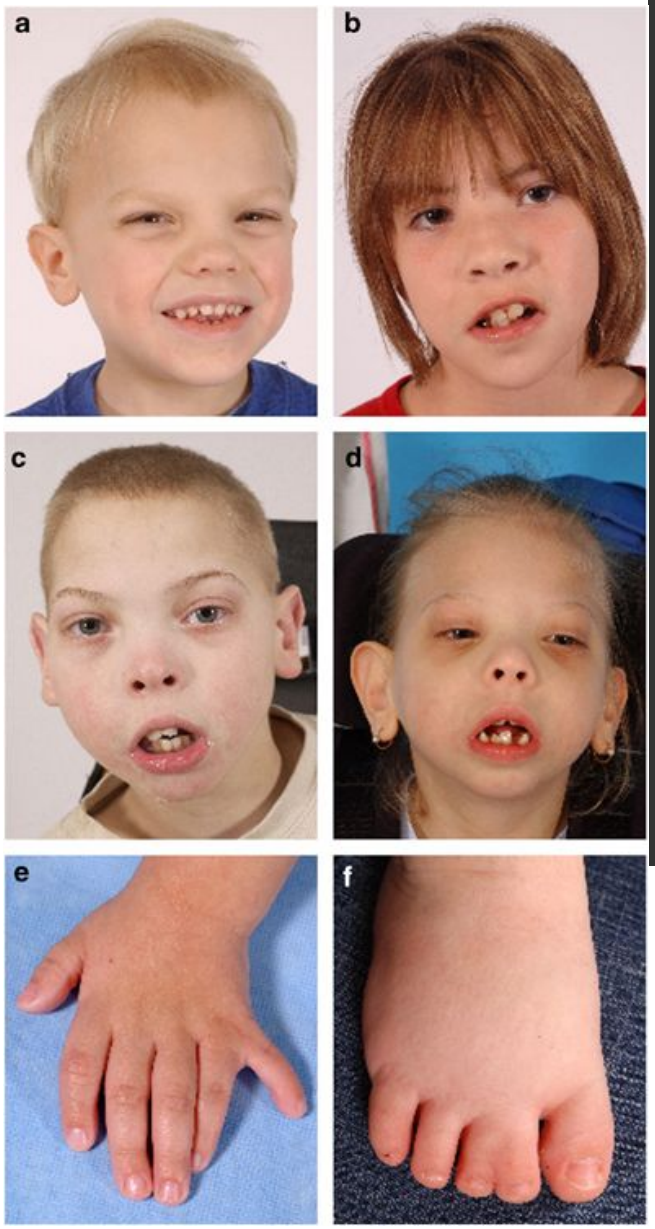
Additional descriptors: It is encouraged to add descriptions of other signs and symptoms, suggested descriptors or free text. These do not alter the seizure type. Example: *focal emotional seizure* with tonic right arm activity and hyperventilation.

Bilateral vs. generalized: Use the term "bilateral" for tonic-clonic seizures that propagate to both hemispheres and "generalized" for seizures that apparently originate simultaneously in both.

Atypical absence: Absence is atypical if it has slow onset or offset, marked changes in tone or EEG spike-waves at less than 3 per second.

Clonic vs. myoclonic: Clonic refers to sustain rhythmical jerking and myoclonic to a regular unsustained jerking.

Eyelid myoclonia: Absence with eyelid myoclonia refers to forced upward jerking of the eyelids during an absence seizure.



Name the syndrome

Mode of inheritance

Enzyme effected

- Smith Lemli Opitz
- AR
- DHCR7 gene
  - *7-dehydrocholesterol reductase*

- Name 6 inherited metabolic diseases associated with strokes or stroke-like episodes

1. Homocystinuria
2. Fabry disease
3. Organic acidopathies (methylmalonic, propionic, isobaleric, glutaric aciduria)
   - Type I and II glutaric aciduraia
4. Ornithine transcarbomoylase deficiency (OTC deficiency)
5. MELAS
6. CDG type 1a
7. Familial hemiplegic migraine

Case

- A child with new onset narcolepsy.

- Name secondary causes of narcolepsy

- Primary brain tumors such as craniopharyngioma
- Head injury
- Encephalitis
- Myotonic dystrophy type 1
- Niemann-Pick disease type C
- NMO

TABLE 11-3

Sleep-Wake Disorders of Childhood

Kotagal, Suresh

CONTINUUM: Lifelong Learning in Neurology23(4, Sleep Neurology):1132-1150, August 2017.

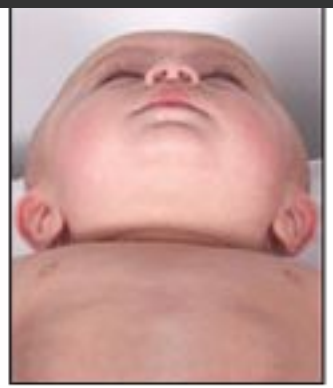
doi: 10.1212/CON.0000000000000504

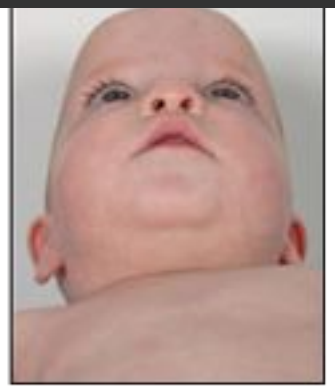
Symptom	Drug	Potential Side Effects
Daytime sleepiness	Methylphenidate	Loss of appetite, suppression of growth, exacerbation of anxiety, nervousness
	Dextroamphetamine, amphetamine-dextroamphetamine mixture	Loss of appetite, suppression of growth, exacerbation of anxiety, nervousness
	Modafinil, armodafinil	Headache, precipitation of Stevens-Johnson syndrome, decreases the potency of concurrently administered oral contraceptives
	Sodium oxybate	Tremor, constipation, bed-wetting, exacerbation of sleep apnea, weight loss, exacerbation of depression
Cataplexy	Sodium oxybate	Tremor, constipation, bed-wetting, exacerbation of sleep apnea, weight loss, exacerbation of depression
	Venlafaxine, protriptyline, clomipramine	Drowsiness, weight gain, tremor
	Fluoxetine, sertraline	Nervousness, insomnia, increased risk of suicidal thoughts
Periodic limb movements	Gabapentin, elemental iron, clonazepam	Drowsiness (with gabapentin and clonazepam), constipation and abdominal discomfort (with iron)

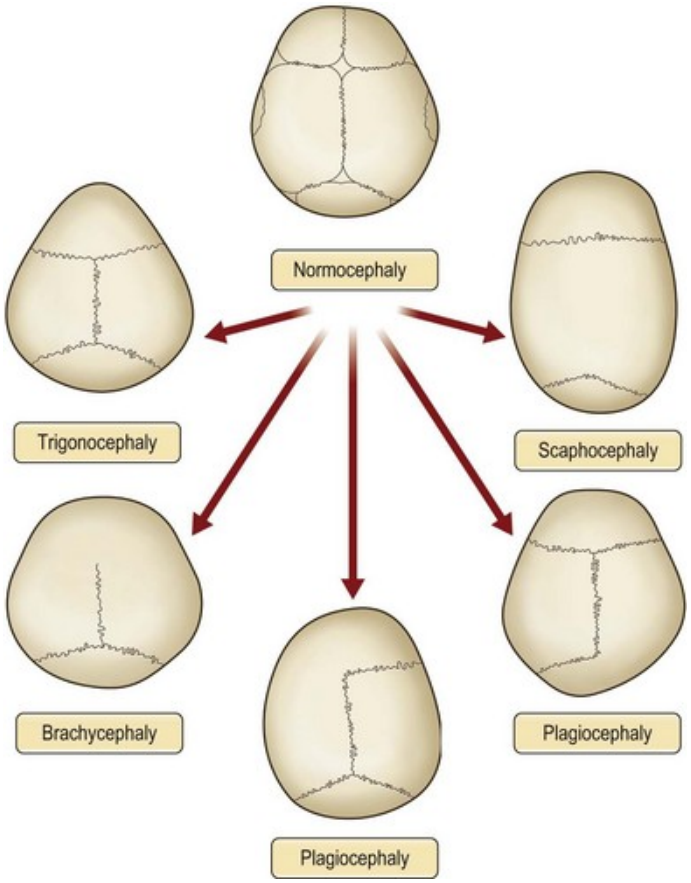
CONTINUUM: LIFELONG LEARNING IN NEUROLOGY

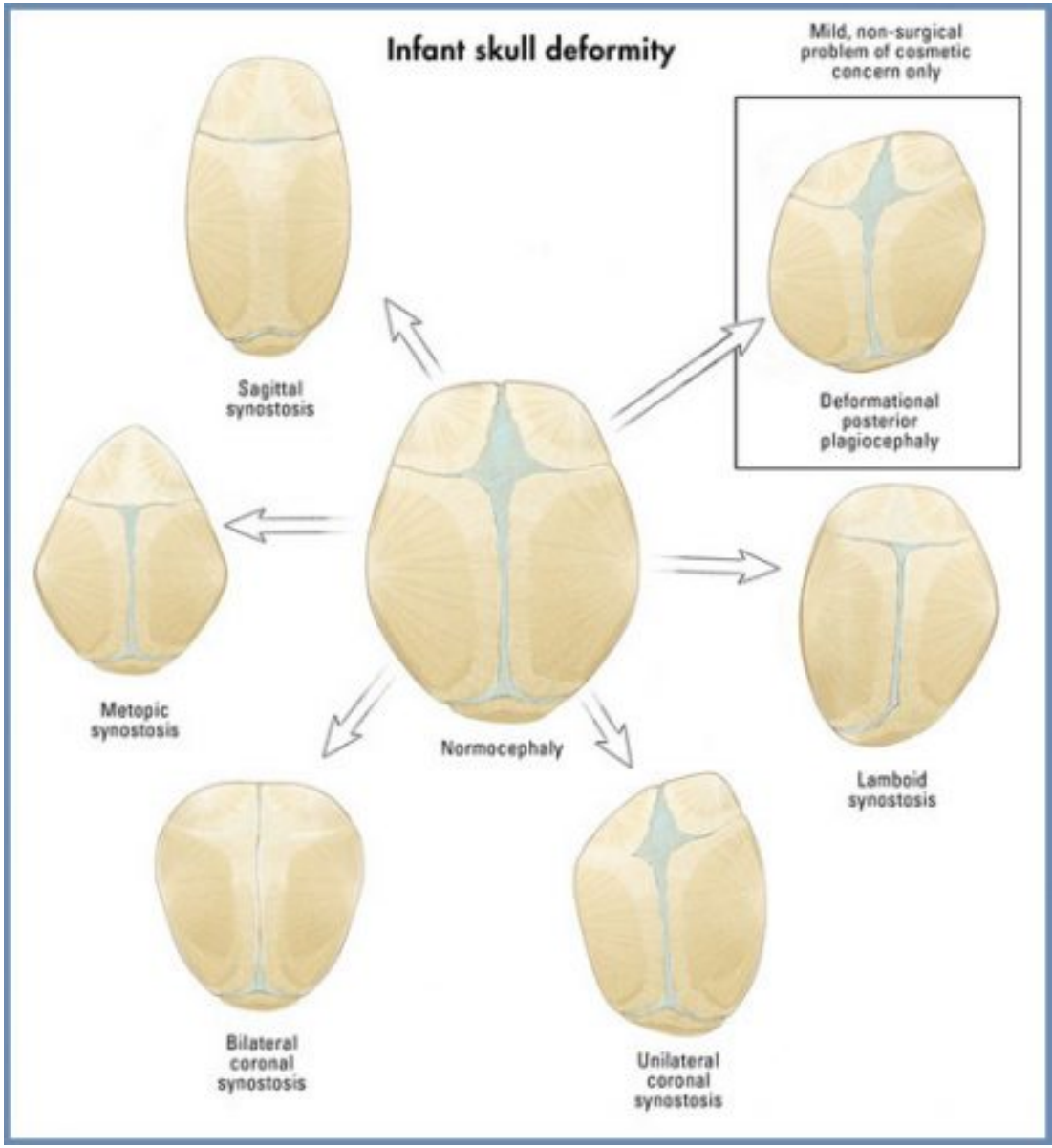
Childhood Narcolepsy Pharmacotherapy

Name the head shape

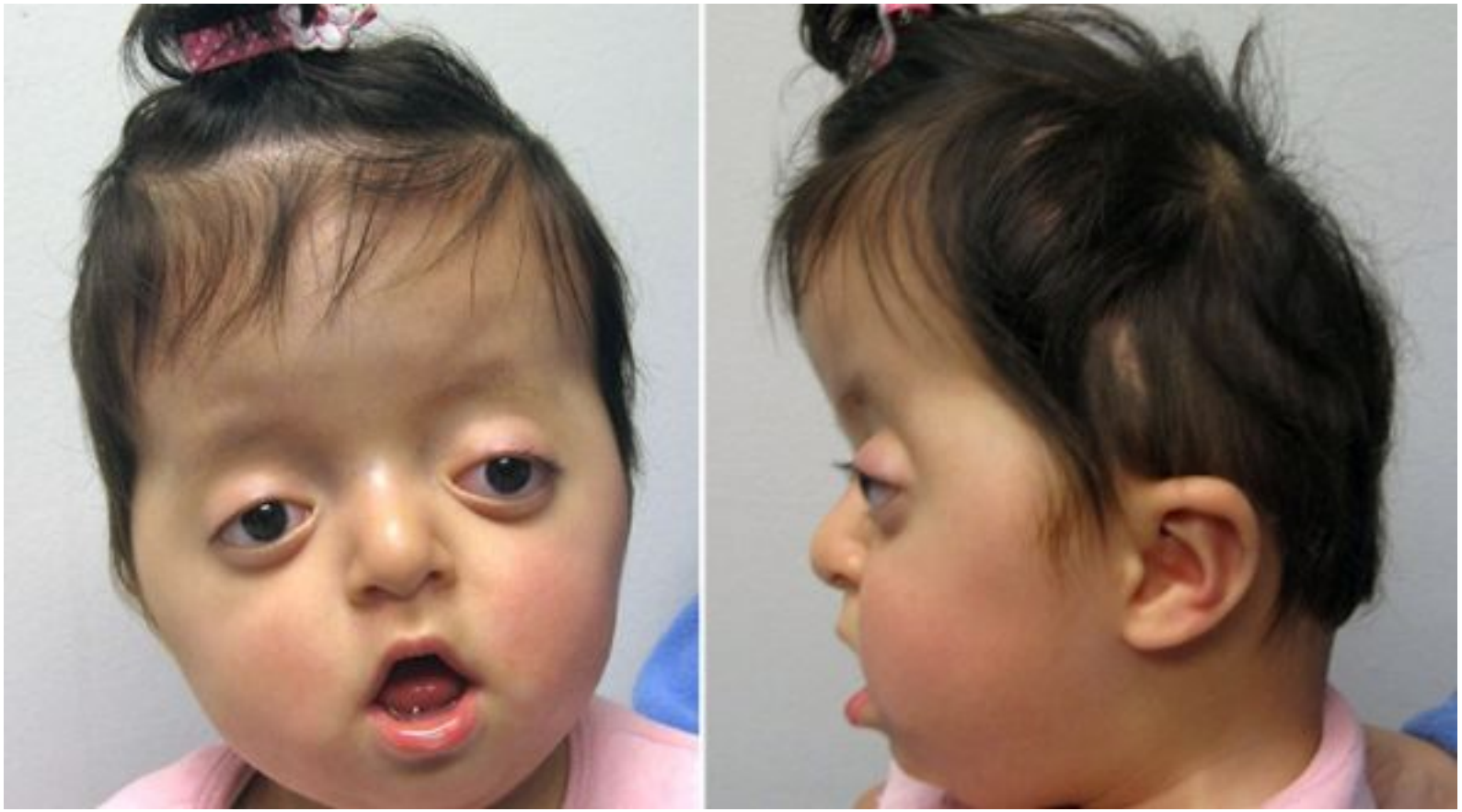





Normocephaly
Trigonocephaly
Scaphocephaly
Brachycephaly
Plagiocephaly
Plagiocephaly


Infant skull deformity
Mild, non-surgical problem of cosmetic concern only
Sagittal synostosis
Deformational posterior plagiocephaly
Metopic synostosis
Normocephaly
Lamboid synostosis
Bilateral coronal synostosis
Unilateral coronal synostosis

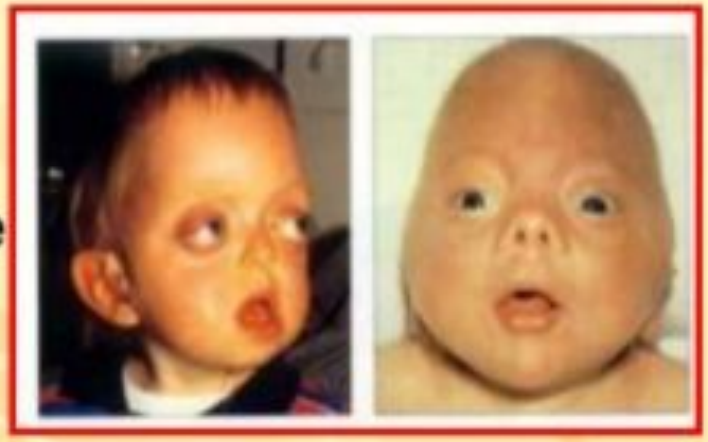
Most common craniosynostosis syndrome?

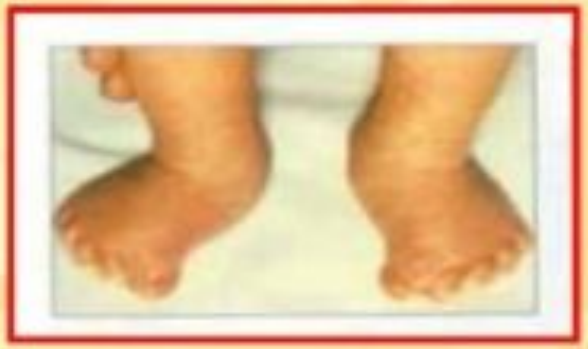


The most common craniosynostosis syndromes are Crouzon, Pfeiffer and Apert.

PFEIFFER SYNDROME

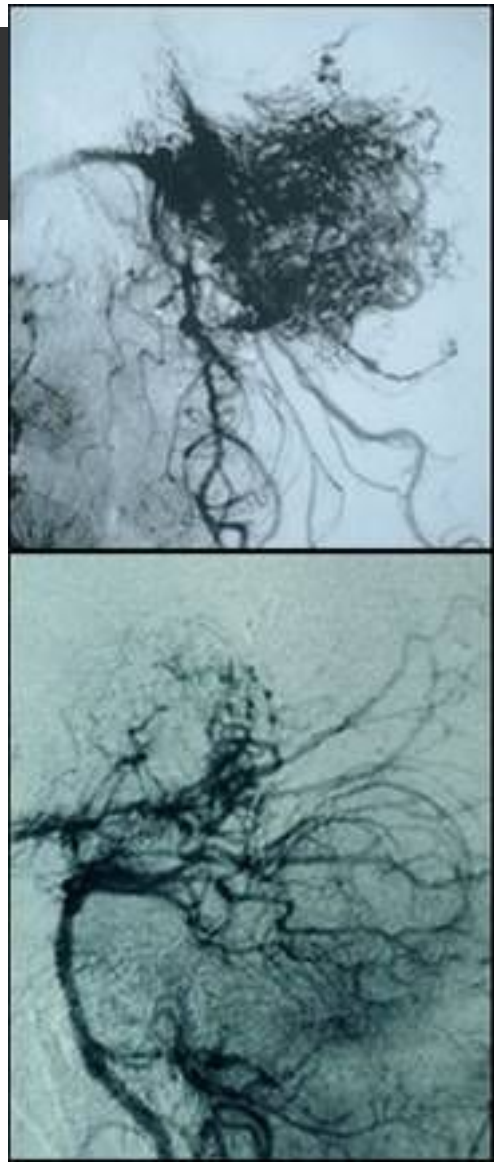
- Generally compatible with life
- Tower Skull
- Normal or near normal intelligence
- Bilateral coronal synostosis
- Midface growth often normal.
- Minimal Ocular proptosis..
- Hydrocephalus is absent.
- Supraorbital ridge recessed.
- Anterior cranial base short and wide
- Orbits are shallow,eyes are proptopic with a degree of hypertelorism
- Syndactyly
- Great toe deviated medially





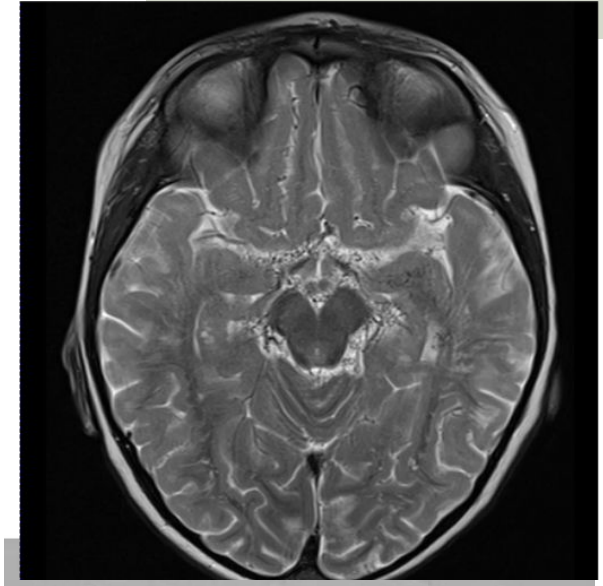
Case

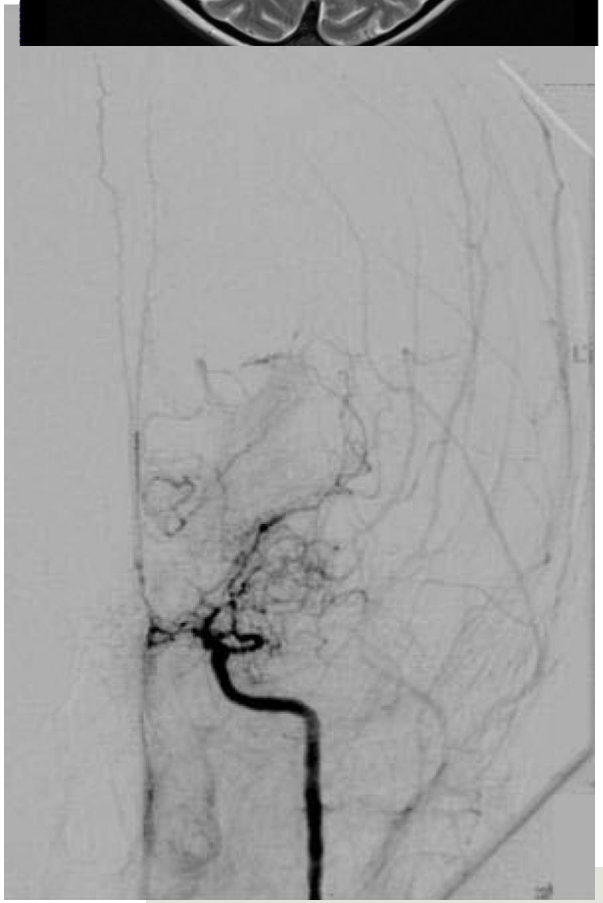
- 23 month old infant with known T21 presents with acute onset hemi-body weakness, with upper motor neuron pattern. Has been unwell for 1 week, now afebrile and no infectious symptoms, but appears dehydrated.
- Angiogram shows the following picture
- What is the most likely diagnosis?



Trisomy 21

- most common chromosomal aneusomy
- characterized by numerous abnormalities including:
  - characteristic facies, heart and gastrointestinal defects, immunological and pulmonary diseases, dermatological problems, epilepsy, ophthalmological and hearing problems, and obesity.
- Neurological features
  - Generalized Hypotonia
  - mental Retardation
  - seizures
  - Moya Moya
  - Dementia
  - cerebral calcifications
  - atlanto-axial instability





Moya Moya

- most frequent cause of stroke in asian children
- progressive narrowing of the distal ICA and proximal circle of Willis with secondary collateralization
- may occur with any progressive vascular occlusion (inherited or acquired)
- Etiology
  - inherited - MYMY1, MYMY2, MYMY3
  - T21, Tuberous sclerosis, Williams syndrome
  - Sickle cell, progeria
  - NF-1 (especially if received radiation)
  - inflammatory - cns angiitis, meningitis
  - vasculopathy - Kawasaki, anticardiolipin antibody, factor V Leyden, polyarteritis nodosa, Behcets SLE

- Clinical features
  - in childhood: TIA, headache, alternating hemiplegia, occasionally DD and poor feeding
  - in adulthood: SAH and intraventricular hemorrhage
  - most frequent cause of stroke in Asian children
  - Natural History: progressive narrowing, colateralization and ischemia, pediatric cases usually advance to stage V within 10 years, hemmorhagic Moya Moya as a poorer prognosis

- Treatment
  - treat underlying disorder (e.g. anticoagulation in prothrombic state)
  - surgical: EDAS - encephalo-duro-arterio-synangiosis

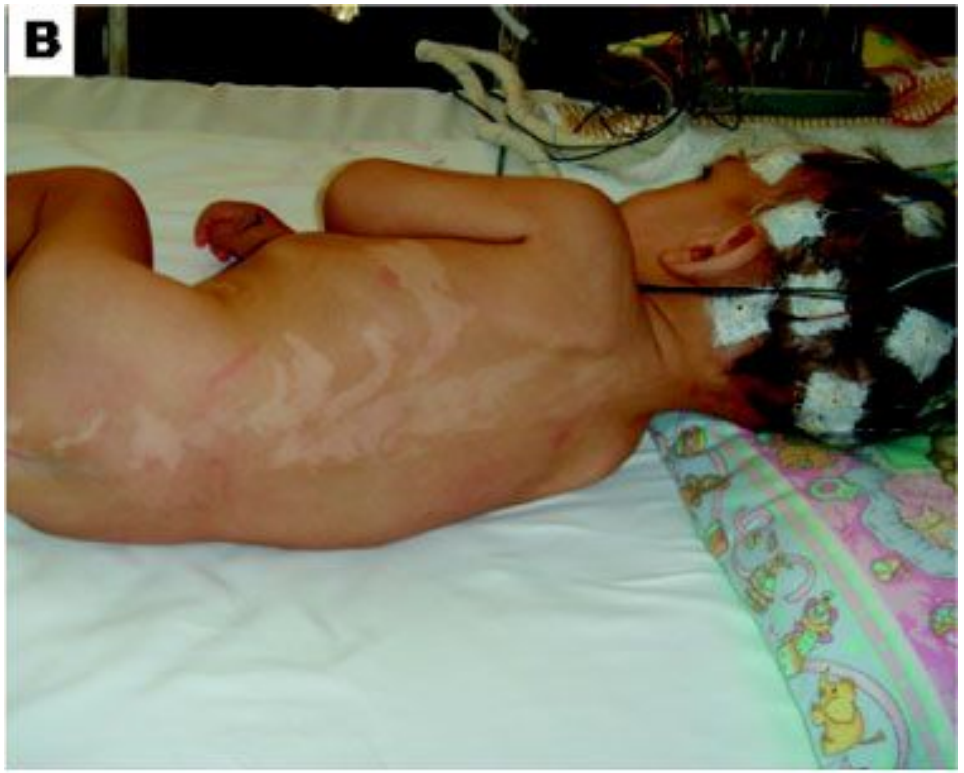
Suzuki stages — Suzuki and colleagues followed patients with moyamoya disease and classified the angiographic progression into six stages [1,83]:

- Stage 1 - Narrowing of carotid fork only
- Stage 2 - Initiation of basal moyamoya with dilatation of all main cerebral arteries
- Stage 3 - Intensification of moyamoya together with reduction of flow in the middle and anterior cerebral arteries
- Stage 4 - Minimization of moyamoya vessels; the proximal portions of the posterior cerebral arteries become involved
- Stage 5 - Reduction of moyamoya and absence of all main cerebral arteries
- Stage 6 - Disappearance of moyamoya vessels; the cerebral circulation is supplied only by the external carotid system

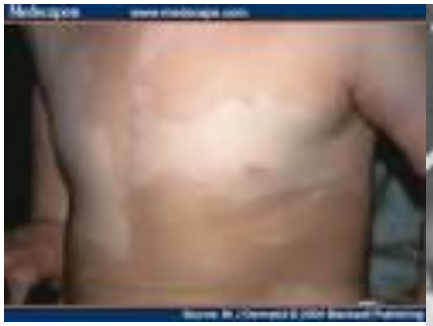
Just a Few Neurocutaneous Conditions

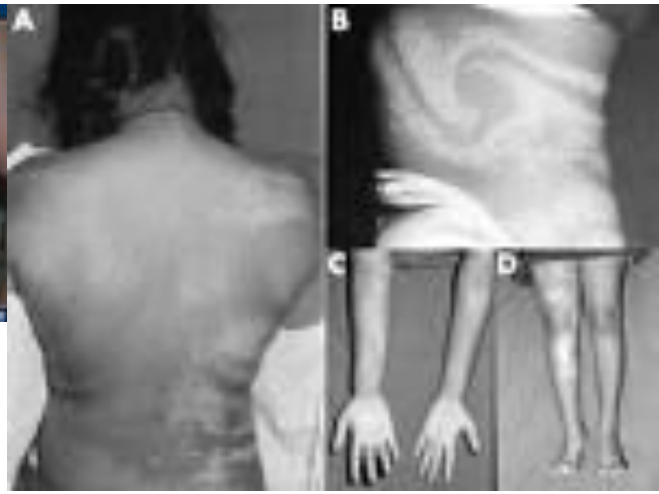
Previously healthy 3 y.o. presents to ER with focal onset seizure with impaired awareness (partial complex seizure).

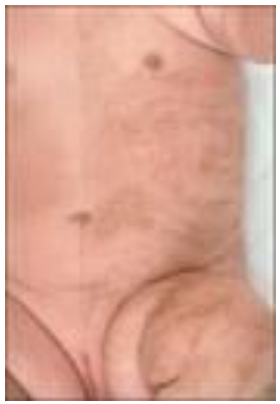
- Diagnosis?
- How inherited?
- Name 3 associated CNS signs/symptoms
- Name 2 other systems that can be involved

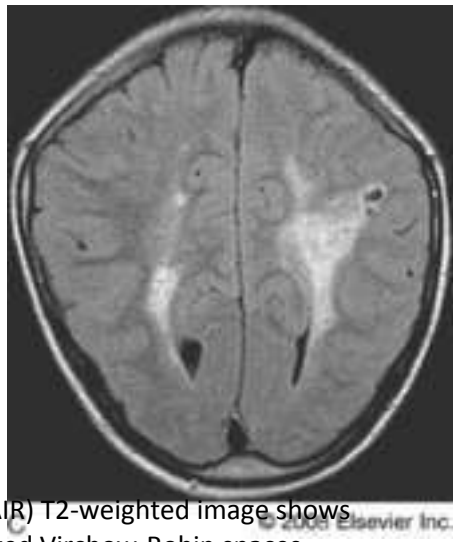


- Diagnosis?
  - Hypomelanosis of Ito
- Gene?
  - Not known, Xp11 locus maybe
  - Mosaicism, multigene?
  - Sporadic or AD inheritance
- Name 3 associated CNS signs/symptoms
  - Hemimegalencephaly (ipsilateral)
  - Macro or microcephaly
  - Seizures
  - MR abN-cortical dysplasia
  - Mental retardation (50%)
  - Higher risk brain tumour
- Name 2 other systems that can be involved
  - Eyes – hypopigmentated
  - MSK – hemihypertrophy, scoliosis
  - Cleft palate
  - Renal
  - Cardiac – cong heart disease
  - Hair – alopecia, thin, hypertrichosis; dental; nails
  - (Genetic – chromosomal abN)

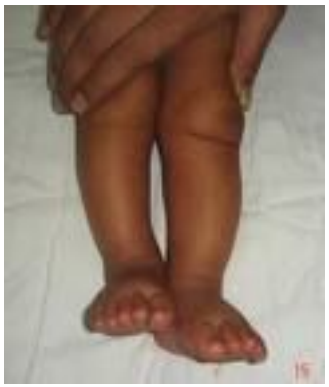


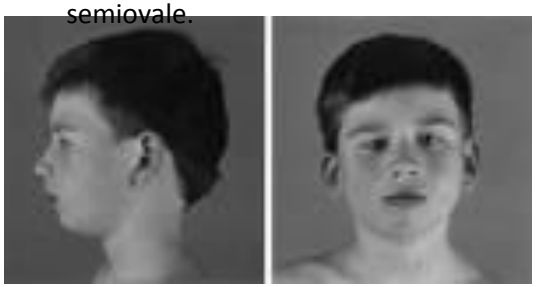




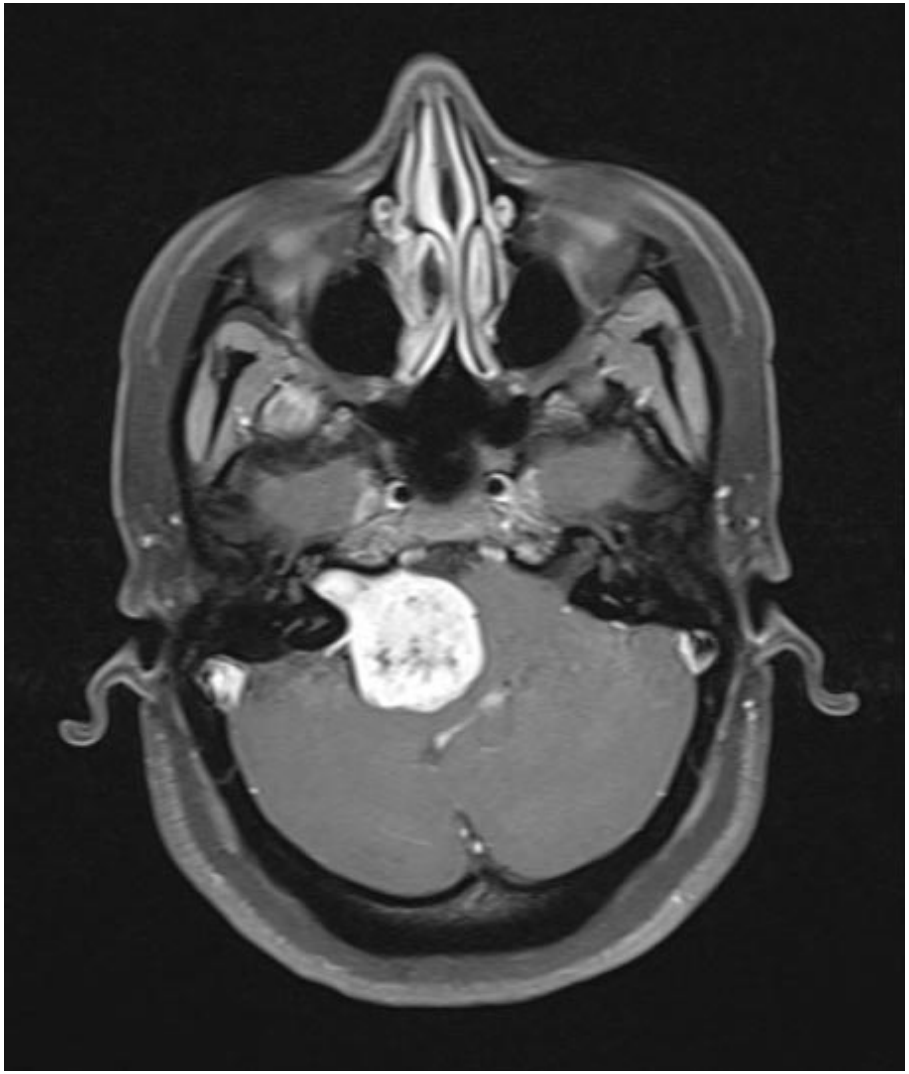


(FLAIR) T2-weighted image shows dilated Virchow-Robin spaces, abnormal myelination of the centrum semiovale.

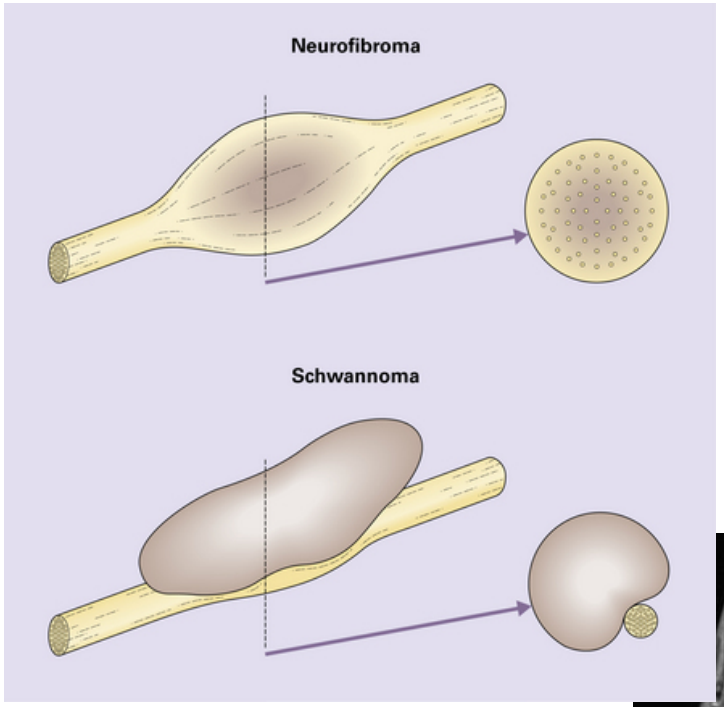




Case: what is this? Suspected diagnosis?

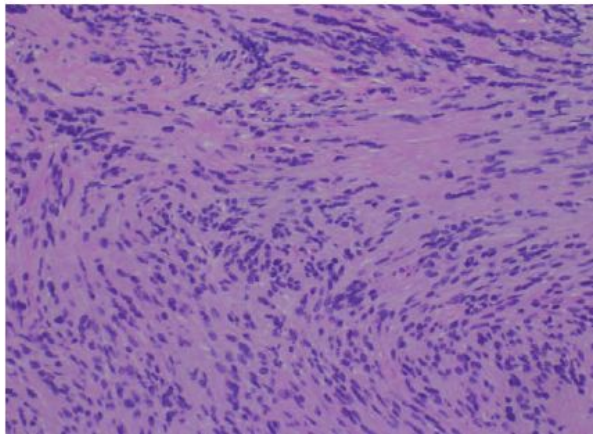


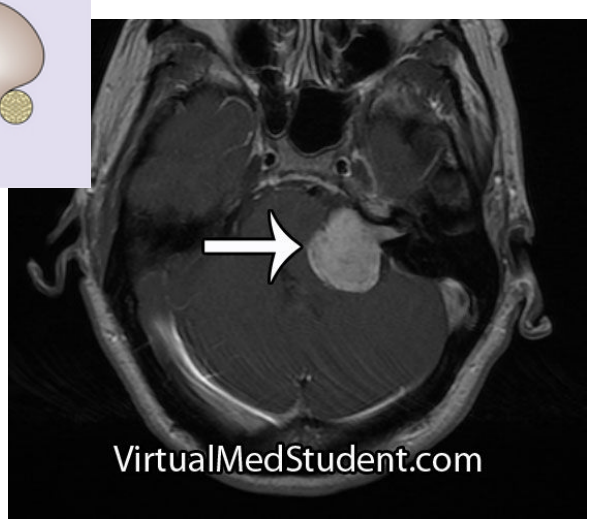
11. Acoustic Schwannoma



Synonyms

- Neurilemoma
- Neurinoma





Schwannomas - Clinical

- Paraspinal
  - Incidental
- Spinal nerve
  - Radicular pain
  - Signs of nerve root/spinal cord compresion
- 8th CN
  - Hearing loss
  - Tinnitus
  - Occasional vertigo
  - Bilateral = hallmark of NF2
    - Pain: think schwannomatosis

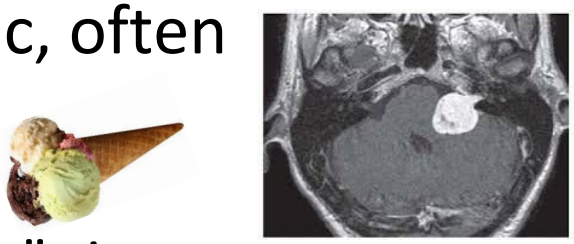
Motor symptoms are **uncommon** 2°/2 schwannomas favoring sensory nerve roots

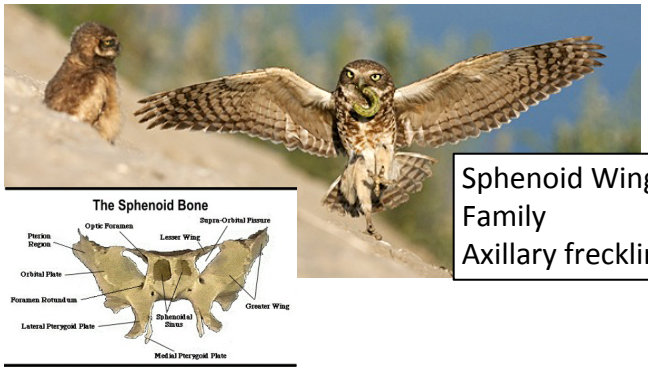
Schwannomas - Imaging

If Schwing-ommas

MRI

- Well circumscribed, sometimes cystic, often heterogenously **enhancing** mass
- Vestibular
  - Often display a classic “ice-cream-cone” sign
    - Tapered intraosseous “cone” exiting in the internal auditory canal, and internal auditory canal expanding out to a rounded cerebellopontine angle mass
- Parasinal and head and neck
  - May be associated with bone erosion (sometimes see on plain x-ray)
  - Paraspinal: may show dumbbell shape (constriction at neural exit foramen

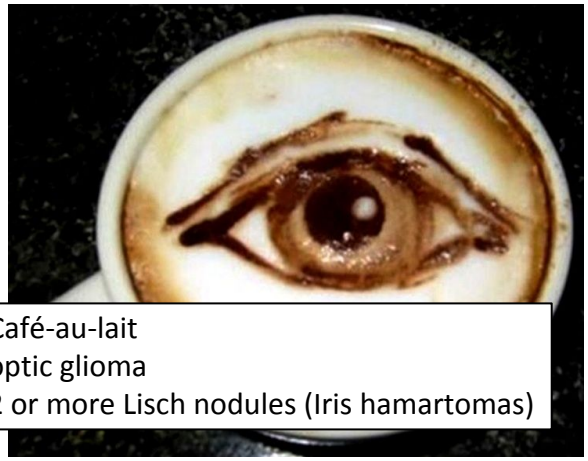




Sphenoid Wing/boney lesion
Family
Axillary freckling

NF-1

Plexiform neurofibroma

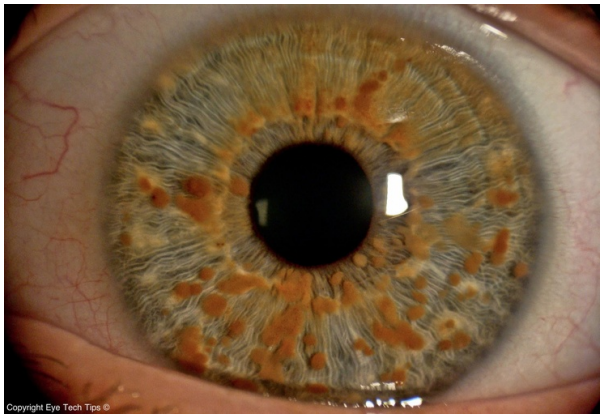


Café-au-lait
optic glioma
2 or more Lisch nodules (Iris hamartomas)

NIH Diagnostic Criteria for NF1

Clinical diagnosis based on presence of **2/7** of the following:

- **6** or more café-au-lait macules over 5 mm in diameter in prepubertal individuals and over 15mm in greatest diameter in postpubertal individuals.
- **2** or more neurofibromas (any type) or **1** plexiform neurofibroma.
- Freckling in the axillary or inguinal regions.
- **2** or more Lisch nodules (iris hamartomas).
- Optic glioma.
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis.
- First-degree relative with NF-1



Diagnostic criteria

CAFE SPOT

Café-au-lait spots.

Axillary or inguinal freckling.

neuro**F**ibroma (two or more) *or* plexiform neuro**f**ibroma (one).

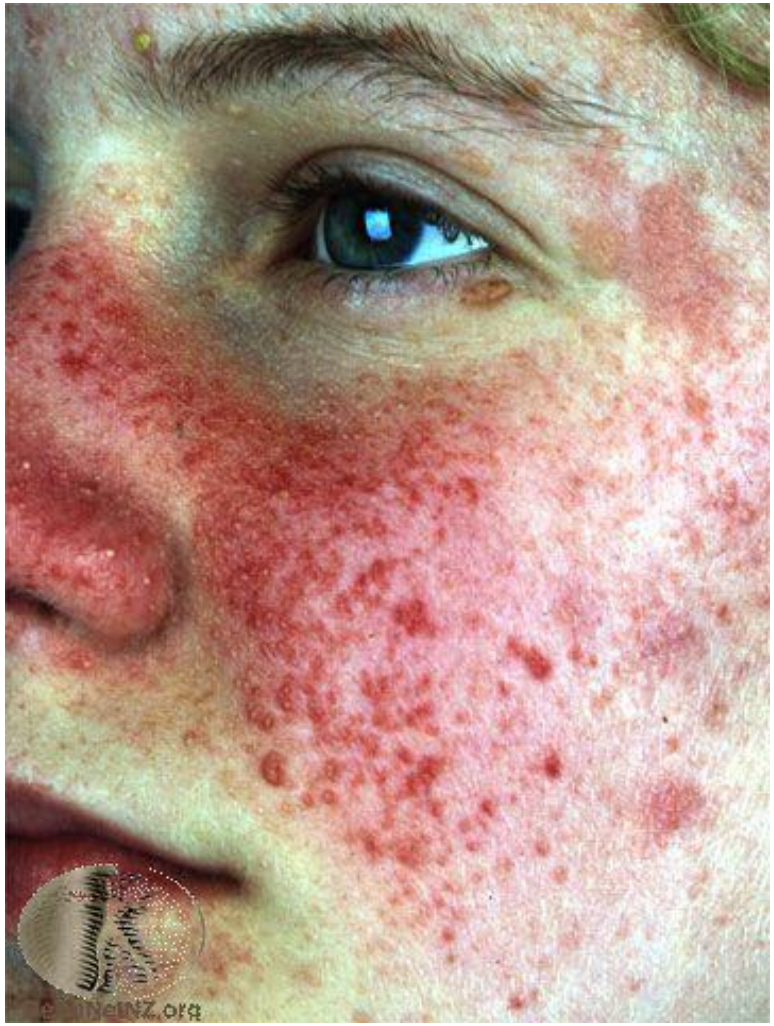
Eye hamartomas (Lisch nodules).

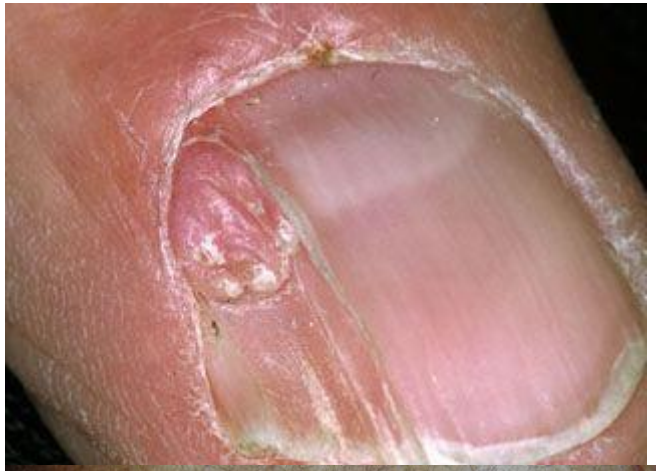
Skeletal abnormalities, e.g. *s*phenoid dysplasia, leg bowing.

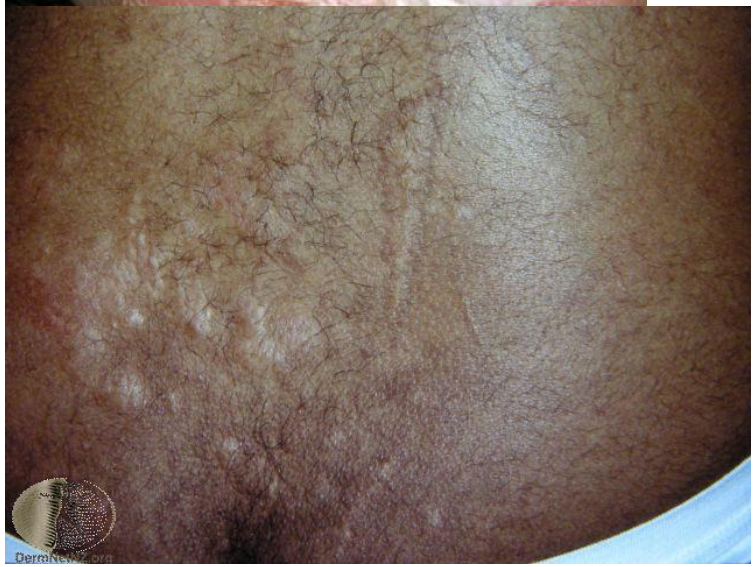
Positive family history. †

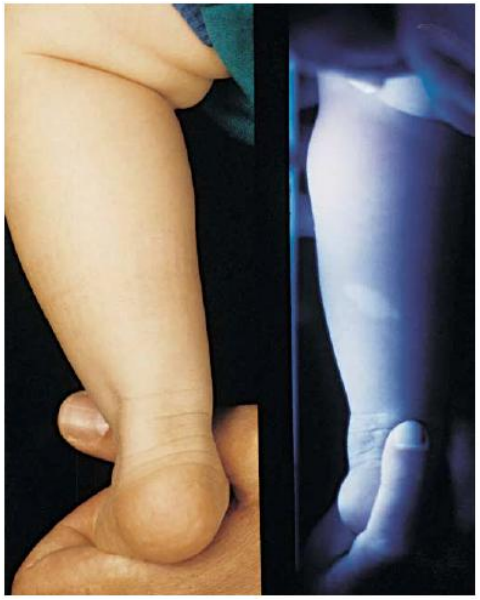
Optic **T**umour (optic nerve glioma)

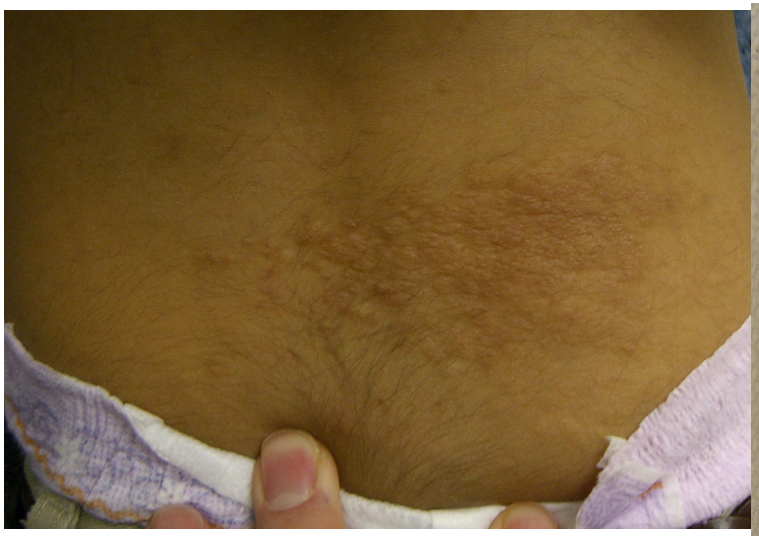
Spot Diagnosis

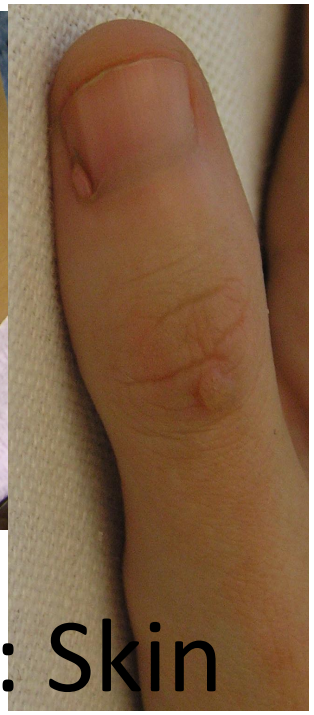


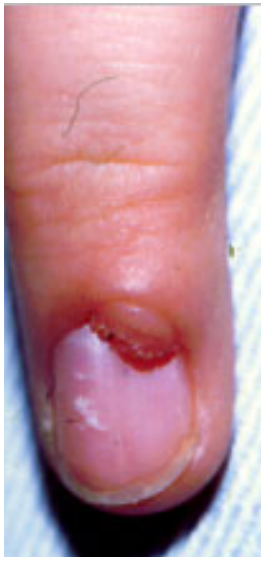




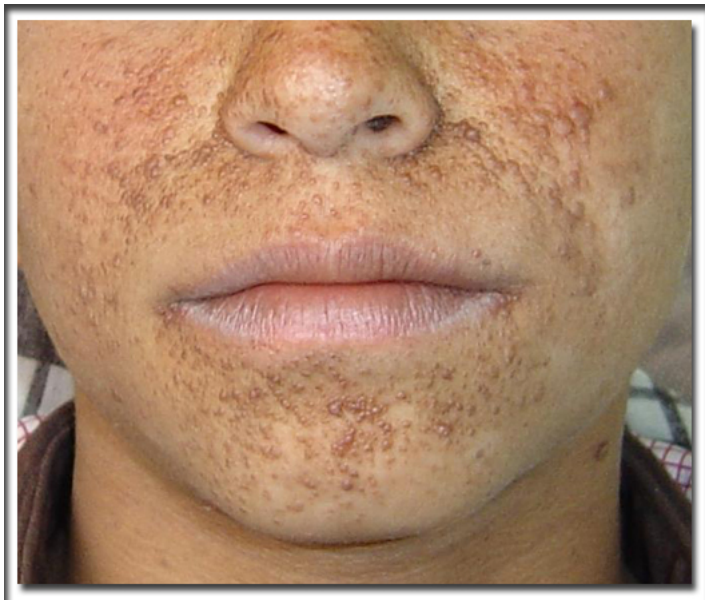


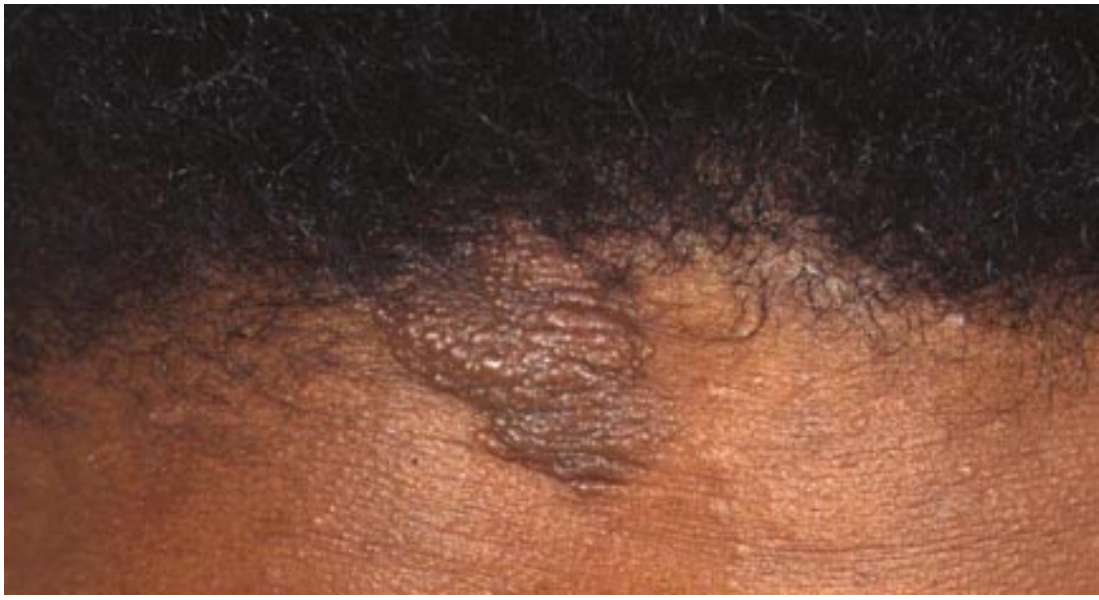






Clinical Features: Skin





Tuberous Sclerosis

Pneumonic – **HAMARTOMAS**

- **H**amartoma (cortical tubers)
- **A**denoma sebaceum
- **M**itral regurgitations
- **A**sh-leaf spots
- **R**habdomyoma
- **T**uberous Sclerosis
- d**O**minant inheritance
- **M**ental retadardation
- **A**ngiomyolipoma (kidney)
- **S**ubependymal nodules, SEGA

Pneumonic – **ASHLEAFS**

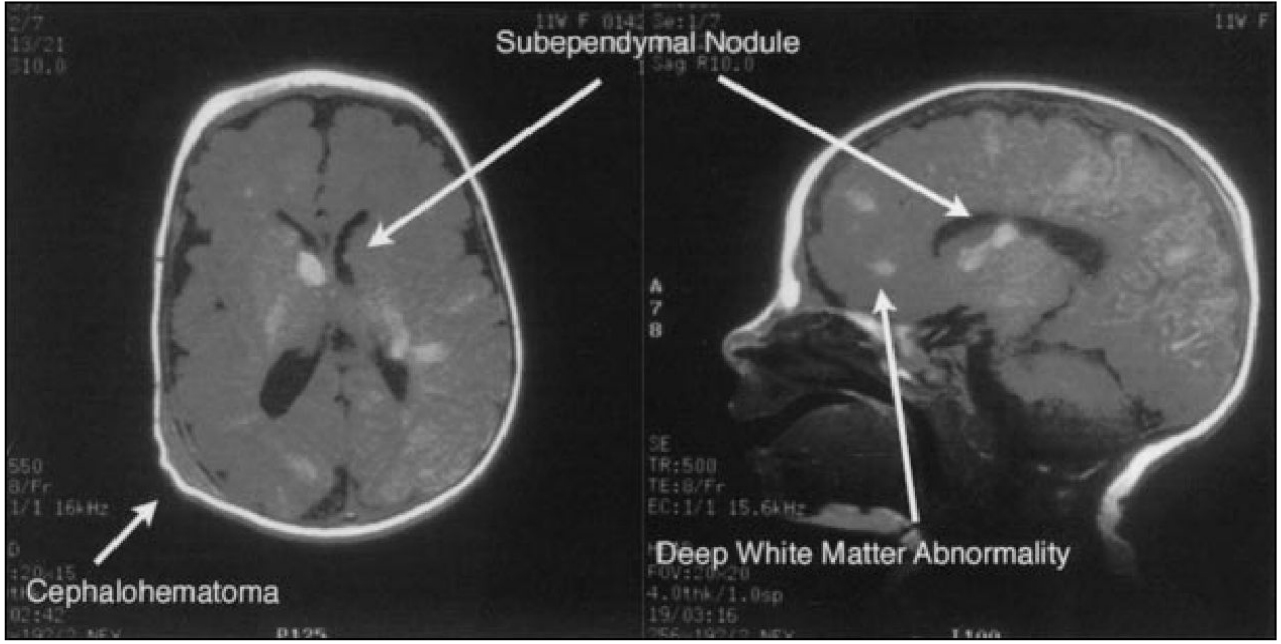
- **A**shleaf spots
- **S**hagreen patches
- **H**eart rhabdomyosarcomas
- **L**ung hamartomas
- **E**pilepsy from cortical tubers
- **A**ngiomyolipoma (kidney)
- **F**acial angiofibroma
- **S**EGA, subependymal nodules

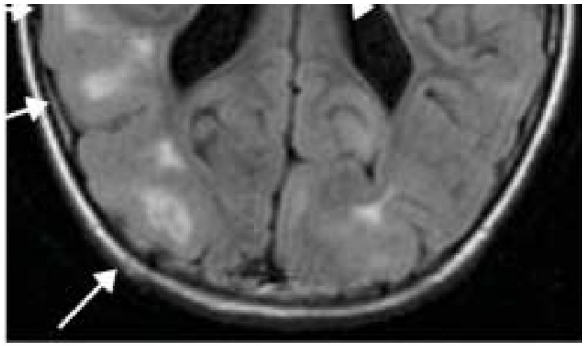
Common findings

CNS
-Learning disability (50%)- autism, ADHD
-Glioneuronal hamartomas (cortical tubers), subependymal nodules, subependymal giant cell astrocytomas
-Mass effect symptoms, such as hydrocephalus and papilledema
-Seizures or infantile spasms. An example can be found HERE.
Kidneys
-Angiomyolipomas (60-80%), renal cysts
-Renal cell carcinoma (rare)
Lungs
-Lymphangioleiomyomatosis (lung parenchyma replacement with cysts)
Heart
-Rhabdomymomas (50%)
SKIN
-Dermatologic sign= 95% of TSC
-Facial angiofibromas, periungual fibromas, hypomelanic macules, forehead plaques, Shagreen patches
-Minimal to no risk of malignant transformation of skin lesions
-Skin lesions tend to increase in size and number through puberty, and then tend to

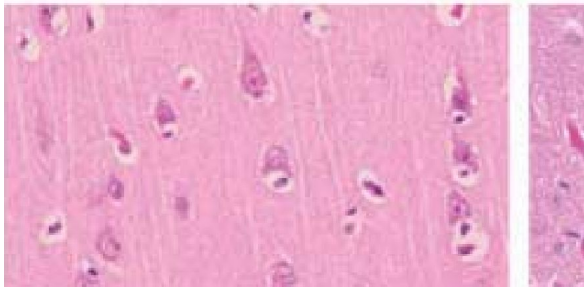
Clinical Features

- Brain
  - Cortical tubers
  - Cortical dysplasia
  - Subependymal nodules [SENs]
  - Subependymal giant cell astrocytomas [SEGAs]
  - Seizures
  - Intellectual disability/developmental delay
  - Autism


Subependymal Nodule
Cephalohematoma
Deep White Matter Abnormality

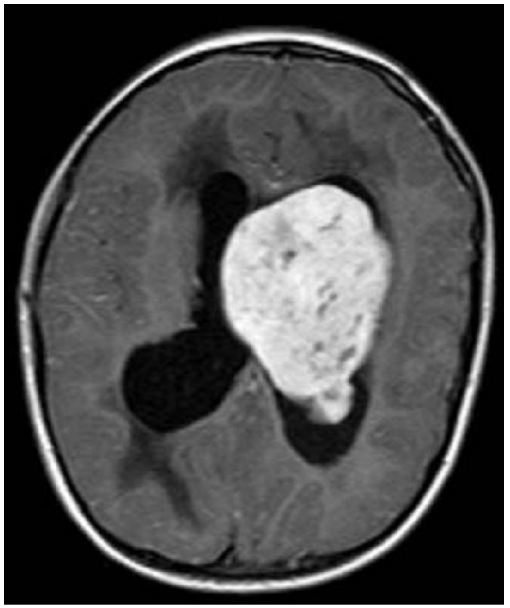


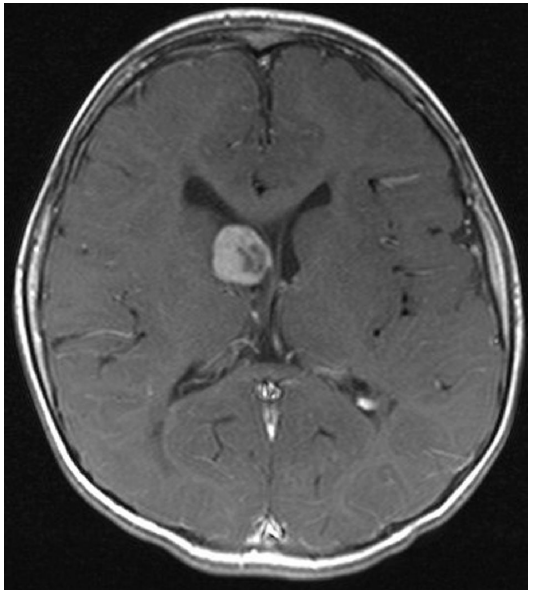
Control



SEGA

- Unilateral or bilateral
- Develop from benign subependymal nodules (hamartomas) near foramen of Monro





Clinical Features

- Heart
  - Rhabdomyomas
  - Arrhythmias
- Lung
  - Lymphangioleiomyomatosis [LAM]
- Kidney
  - Angiomyolipomas
  - Cysts
  - Renal cell carcinomas

Diagnostic Criteria: Clinical

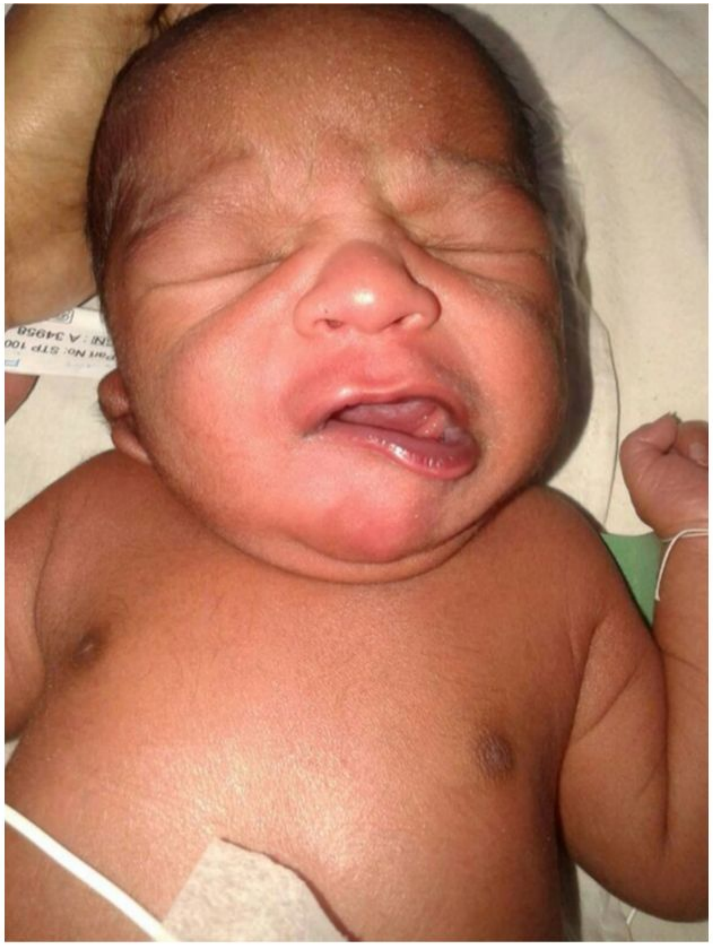
Major Features	Minor Features
Facial angiofibromas or forehead plaque	Multiple randomly distributed pits in dental enamel
Nontraumatic ungal or periungal fibromas	Hamartomatous rectal polyps
Hypomelanotic macules (≥3)	Bone cysts
Shagreen patch (connective tissue nevus)	Cerebral white matter radial migration lines
Multiple retinal nodular hamartomas	Gingival fibromas
Cortical tuber	Nonrenal hamartomas
Subependymal nodule	Retinal achromic patch
SEGA	Confetti skin lesions
Cardiac rhabdomyomas	Multiple renal cysts
Lung Lymphangioleiomyomatosis (LAM)	
Renal angiomyolipoma	

Definite Diagnosis
□2M or 1M +2m

Probable
□1M +1m

Possible
□1M or ≥2m

Thanks Kim Smyth



1. What is the exam finding and underlying defect?

1. List a differential diagnosis for this finding

1. What syndrome is associated with this finding?

1. Name one genetic and one non-genetic investigation you would order for this child.

Answer slide

1. What is the exam finding and underlying defect?
   - Asymmetric crying face, absence or hypoplasia of depressor anguli oris muscle

Image source:

Iran J Pediatr. 2015 April; 25(2):e502. DOI: 10.5812/ijp.502
Published online 2015 April 18. Case Report

Cayler Cardio-Facial Syndrome: An Uncommon Condition in Newborns

Sunil Jayaram Pawar [1]; Deepak Kumar Sharma [2,*]; Sela Srilakshmi [1]; Suguna Reddy Chejeti [1]; Aakash Pandita [2]

Answer Slide

1. Differential Diagnoses for Newborn with asymmetric crying facies (NACF)?
   - Rule out UMN pattern weakness (stroke)
   - Cranial Nerve 7 injury (i.e. traumatic >>>Bell's palsy, tumor/mass)
   - Developmental facial paralysis: Mobius Syndrome, GoldenHar Syndrome
   - NACF (really is its own distinct diagnoses referring to hypoplasia of depressor anguli oris muscle)

1. What syndromes are associated with this finding?
   - 22q11 deletion (14%)
   - Cayler Cardiofacial Syndrome
   - Rare associations with neuroblastoma, NF1 reported

1. Name one genetic and one non-genetic investigation you would order for this child.
   - **ECHO and genetic test for 22q11.2 deletion (FISH)**
     - Also hearing test
     - Could consider B-scan ultrasound to confirm absence of muscles?

Hypoplasia Depressor Anguli Oris

- Lin et al.(1997): 50 patients with hypoplasia
  - 70% had other anomalies
    - Head/neck (48%), heart 44%, MSK 22%, GU 24%, CNS 10%, GI 6%, FTT 10%, psychomotor retardation 6% (3)
- Casken et al. 2004: 35 cases
  - 45% had other anomalies
    - Cerebral/cerebellar atrophy, mental and motor retardation, MSK, GU, cranial bone defects

Cayler Syndrome

- Absence or hypoplasia of depressor anguli oris muscle plus
- Cardiac defect
  - ASD or VSD> Tetrology Fallot
- Rarely microcephaly, micrognathia, microphthalmos, mental retardation
- Typically Autosomal Dominant inheritance
- Cayler Syndrome is most commonly associated with being part of 22q11 deletion syndrome (along with DiGeorge, velocardiofacial syndromes, Goldenhar) ….
- I.e. it is a spectrum

Headaches

- https://www.ichd-3.org/

Did you **SNOOP** for the headache red flags?

Systemic symptoms (fever, wt loss, persistent or progressive vomiting, stiff neck, pregnancy, cancer, immunocompromised state, anticoagulated)

Neurologic symptoms (or abnormal signs – confusion, impaired alertness or consciousness)

Onset: sudden, abrupt, or split-second

Older: new onset and progressive headache, especially in middle age >50 (GCA)

Previous headache history: first headache or different (change in attack frequency, severity, or features)

- All treatments: remember pharmacologic, non-pharmacologic, multidisciplinary treatments, and follow-up plan

Case

- 2 year old, otherwise well, developmentally normal child
- Stubs toe while running
- Sudden cessation of activity, turns pale, falls to the floor, and has generalized tonic then clonic activity for 15-20 seconds
- Returns to baseline rapidly

- Most likely diagnosis?

Breath holding spells

- Brief episodes of change in autonomic function with loss of consciousness in toddlers.
- Benign, non volitional, paroxysmal events
- Seen in approximately 5% of children. Family history in 20-35%. Cyanotic more common
- Are cyanotic and pallid forms. Commonly present at 6 to 18 months with variable frequency. Resolves by 3 to 4 years; rare over 6 years.
- Usually precipitated by brief (15sec) crying in response to pain, anger, frustration or minor trauma followed by cessation of breathing and child then goes limp. In some cases short anoxic-clonic seizures may follow.
- Pallid are more associated with sudden pain or fright. Child lets out a brief gasp then becomes pale during a short loss of consciousness. The body stiffens and brief clonic jerks can be seen. Spell lasts less than 1 minute. Child more likely to be fatigued or sleep afterwards.

Two types of breath-holding spells	
Pallid: child turns a pale color	Cyanotic: child turns a blue color, especially around the lips
Characteristics include: ▪ Triggered by sudden fright or pain or falling with a minor injury to the head ▪ Child may gasp and give a brief cry ▪ Child becomes pale, loses consciousness and becomes limp ▪ Child may become sweaty and may stiffen and have a few body jerks or lose bladder control ▪ Episodes are brief and last less than one minute ▪ Child regains consciousness and will recognize people but can seem sleepy	Characteristics include: ▪ Triggered by becoming frustrated or angry ▪ The child may cry vigorously, usually less than 15 seconds ▪ After crying, the child becomes silent, stops breathing, and rapidly turns blue ▪ The child usually loses consciousness, goes limp, or stiffens and arches his back ▪ Recovery happens in less than one minute ▪ May gasp and return to regular breathing ▪ Regain consciousness and returns to normal ▪ May seem tired ▪ It is rare for the child to be upset and cry again triggering another episode

Investigations

- CBC
- iron studies
- EEG - if frequent consider video monitoring
- EKG +/- echocardiogram
- Imaging not warranted unless worsening and not responding to treatment. or associated with other abnormalities.

Treatment

- Education and support
- Iron supplementation: ferrous sulfate, 5-6mg/kg/day (elemental)
- 5mg/kg of elemental ferrous sulfate divided tid.
- Liquid ferrous sulfate- Fer in sol is liquid with 150mg/ml. = 30 mg elemental fe / ml. Can Give in water or juice.
- 300mg of ferrous sulfate = 60 mg elemental iron (20%)

Iron for breath holding spells:

- To investigate the effect of iron therapy breath holding spells, in a clinical trial 41 children were give ferrous sulfate solution orally in a dosage of 6 mg/kg per day for 3 months. At the end of this period 28 patients had taken the medication regularly. 21 (75%)of children showed no more spells, 4(14%) responded moderately (more than 50% reduction in attacks/month), and 3 (11%) poorly (less than 50% reduction in attacks/ month) to the therapy. Results of this study confirm that iron therapy is effective in the treatment of breath holding spells. (Cochrane review)

Case

- 15 y/o otherwise healthy F, singing at an assembly, slumps to the ground slowly, and found to have generalized convulsions with incontinence
- After the event, she endorses ocular phenomenon preceding the event, including tunnel vision.

- https://youtu.be/DOHGXoiS_Dk

Some diagnostic criteria for fun

MECP2

- Diagnostic criteria:
  - The diagnosis should be considered when there is postnatal deceleration of head growth observed (but not mandatory)
  - Required for typical/classic Rett syndrome
    - A period of regression followed by recovery or stabilization
    - All of the main criteria and all of the exclusion criteria
      - Supportive criteria are not required, although often present
  - Required for atypical or variant Rett syndrome
    - A period of regression followed by recovery or stabilization
    - 2 of the 4 main criteria
    - 5 of the 11 supportive criteria
- Main criteria
  - Partial or complete loss of acquired purposeful hand skills
  - Partial or complete loss of acquired spoken language or language skill (babble).
  - Gait abnormalities: impaired (dyspraxic) or absence of ability
  - Stereotypic hand movements: hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms
- Exclusion criteria for typical Rett syndrome
  - Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection
  - Grossly abnormal psychomotor development in the 1st 6 months of life, with early milestones not being met
- Supportive criteria for atypical Rett syndrome (currently or at any time)*
  - Breathing disturbances when awake
  - Bruxism when awake
  - Impaired sleep pattern
  - Abnormal muscle tone
  - Peripheral vasomotor disturbances
  - Scoliosis/kyphosis
  - Growth retardation
  - Small cold hands and feet
  - Inappropriate laughing/screaming spells
  - Diminished response to pain
  - Intense eye communication - “eye pointing”

TABLE

Updated diagnostic criteria for tuberous sclerosis complex 2012

A. Genetic diagnostic criteria

The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

B. Clinical diagnostic criteria

Major features

1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)†
11. Angiomyolipomas (≥2)†

Minor features

1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥2 minor features

Possible diagnosis: Either one major feature or ≥2 minor features

* Includes tubers and cerebral white matter radial migration lines.

† A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

Box 40-5 Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibroma
- Hypopigmented macules (more than 3)
- Shagreen patch (connective tissue nevus)
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Multiple retinal nodular hamartomas
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor Features

- Dental pits (more than 14), randomly distributed
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Nonrenal hamartomas
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts

Diagnostic Certainty Criteria

Definite TSC

- 2 major features or
- 1 major feature + 2 minor features

Probable TSC

- 1 major feature + 1 minor feature

Possible TSC

- 1 major feature or
- 2 or more minor features

(From Roach ES et al. Tuberous sclerosis complex consensus conference: Revised clinical diagnostic criteria. J Child Neurol 1998;13(12):624–8.)

Table 2 - Diagnostic criteria for Neurofibromatosis type 1 (NF1) established by the National Institutes of Health Consensus Development Conference (1988)[15]

Individual is affected with NF1 if two or more of the following conditions are met:

- Six or more café au lait macules over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals.
- Two or more neurofibromas of any type, or one plexiform neurofibroma.
- Freckling in the axillary or inguinal regions.
- Optic glioma.
- Two or more Lisch nodules (iris hamartomas).
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudoarthrosis.
- A first-degree relative with NF1 by the above criteria.

Box 40-3 Diagnostic Criteria for Neurofibromatosis 2

Confirmed NF2*

- Bilateral vestibular schwannomas
  or
- A first-degree relative with NF2
  and either
- Unilateral vestibular schwannoma before age 30 years
  or any two of
- Meningioma, schwannoma, ependymoma, juvenile lens opacity

Presumptive NF2

- Unilateral vestibular schwannoma before age 30 years and at least one of: meningioma, schwannoma, ependymoma, juvenile lens opacity
  or
- Two or more meningiomas and unilateral vestibular schwannoma before age 30 years or at least one of: meningioma, schwannoma, ependymoma, juvenile lens opacity

Manchester Criteria†

- Bilateral vestibular schwannomas
  or
- A first-degree relative with NF2
  and either
- Unilateral vestibular schwannoma or any two of: meningioma, schwannoma, ependymoma, neurofibroma, posterior subcapsular lenticular opacity
  or
- Unilateral vestibular schwannoma and any two of: meningioma, schwannoma, ependymoma, neurofibroma, posterior subcapsularlenticular opacity
  or
- Two or more meningiomas and unilateral vestibular schwannoma or any two of: meningioma, schwannoma, ependymoma, neurofibroma, posterior subcapsular lenticular opacity

(*Based on*
* Gutmann DH et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997;278: 51–57.
† Baser ME et al. Evaluation of clinical diagnostic criteria for neurofibromatosis 2. Neurology 2002;59(11):1759–1765.)

Box 40-4 Diagnostic Criteria for Schwannomatosis

- Patient does not fulfill diagnostic criteria for NF2, and has no vestibular schwannoma on high-resolution MRI and no *NF2* mutation

Definite Diagnosis

- Age over 30 years AND two or more nonintradermal schwannomas, at least one with histologic confirmation
  or
- One pathologically confirmed schwannoma plus a first-degree relative who meets the above criteria

Possible Diagnosis

- Age under 30 years AND two or more nonintradermal schwannomas, at least one with histologic confirmation
  or
- Age over 45 years AND two or more nonintradermal schwannomas, at least one with histologic confirmation
  or
- Radiographic evidence of a schwannoma and first-degree relative meeting the criteria for definite schwannomatosis

Segmental

- Meets criteria for either definite or possible schwannomatosis but limited to one limb, or five or fewer contiguous segments of the spine

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(From MacCollin M et al. Diagnostic criteria for schwannomatosis. Neurology 2005;64(11):1838–1845; Baser ME et al. Increasing the specificity of diagnostic criteria for schwannomatosis. Neurology 2006;66(5):730–732.)

TABLE 2 Diagnostic Criteria: PHACE Syndrome

PHACE Syndrome		
Facial Hemangioma >5 cm in diameter PLUS 1 Major Criteria OR 2 Minor Criteria		
Possible PHACE Syndrome		
Facial Hemangioma >5 cm in diameter PLUS 1 Minor Criteria	Hemangioma of the Neck or Upper Torso PLUS 1 Major Criteria OR 2 Minor Criteria	No Hemangioma PLUS 2 Major Criteria
Organ System	Major Criteria	Minor Criteria
Cerebrovascular	Anomaly of major cerebral arteries Dysplasia[a] of the large cerebral arteries[b] Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate to severe hypoplasia of the large cerebral arteries Aberrant origin or course of the large cerebral arteries[b] Persistent trigeminal artery Saccular aneurysms of any cerebral arteries	Persistent embryonic artery other than trigeminal artery Proatlantal intersegmental artery (types 1 and 2) Primitive hypoglossal artery Primitive otic artery[c]
Structural brain	Posterior fossa anomaly Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia	Enhancing extra-axial lesion with features consistent with intracranial hemangioma[c] Midline anomaly[d] Neuronal migration disorder[e]
Cardiovascular	Aortic arch anomaly Coarctation of aorta Dysplasia[a] Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch (double aortic arch)
Ocular	Posterior segment abnormality Persistent fetal vasculature (persistent hyperplastic primary vitreous) Retinal vascular anomalies Morning Glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma Coloboma	Anterior segment abnormality Sclerocornea Cataract Coloboma Microphthalmia
Ventral or midline	Sternal Defect Sternal cleft Supraumbilical raphe Sternal defects	Hypopituitarism Ectopic thyroid

[a] Includes kinking, looping, tortuosity, and/or dolichoectasia.
[b] Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
[c] See Structural Brain Anomalies section for discussion.
[d] Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia.
[e] Polymicrogyria, cortical dysplasia, or gray matter heterotopia.

Provisional Tic

- Single or multiple motor and/or vocal tics are present
- The tics have been present for less than 1 year since the first tic onset
- The onset is before age 18 years
- The disturbance is not due to the direct physiologic effects of a substance (eg, stimulants) or a general medical condition (eg, Huntington disease or postviral encephalitis)
- Criteria have never been met for Tourette's disorder or persistent (chronic) motor or vocal tic disorder

Persistent (chronic) tic

- Single or multiple motor or vocal tics, but not both, have been present at some time during the illness
- The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset
- The onset is before age 18 years
- The disturbance is not due to the direct physiologic effects of a substance (eg, cocaine) or a general medical condition (eg, Huntington disease or postviral encephalitis)

- Criteria have never been met for Tourette's Disorder

Tourettes

- Both multiple motor and 1 or more vocal tics have been present at some time during the illness, though not necessarily concurrently.
- The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset
- The onset is before age 18 years
- The disturbance is not due to the direct physiologic effects of a substance (eg, cocaine) or a general medical condition (eg, Huntington disease or postviral encephalitis)