DYSMORPHIC SYNDROMES/CASE BASED APPROACH

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Objectives

- Understand different inheritance patterns
- Recognize management options for various syndromes
- Identify common clinical features of Marfan syndrome, Duchenne's muscular dystrophy, Beckwith Wiedemann syndrome, Neurofibromatosis type I and Smith-Lemli-Opitz

Genetic Disorders

- Inherited disorders are diagnosed in individuals of all ages.
- Some inherited disorders are diagnosed during childhood.
- Many inherited disorders do not present until adulthood.
- Diagnosing these disorders is important in both management and anticipation of complications in the patient as well as diagnosing asymptomatic family members.

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A 40 year old male had a lesion on his abdomen removed. Pathology identified the lesion as a Neurofibroma. On physical exam the patient has 10 café au lait spots and axillary freckling.

Which is the most likely diagnosis?
A. Tuberous Sclerosis
B. Noonan syndrome
C. Neurofibromatosis Type I
D. Neurofibromatosis Type II
E. Klinefelter Syndrome

Patient A

A 40 year old man notices a few raised lesion on his abdomen and 2 lesions on his legs.

He had many brown spots on his trunk and limbs. He states he has had these spots since childhood.

Family History

The patient has 2 children ages 10, 12.
He has 2 brothers, one has similar spots.
His mother is 65, healthy
His father died from complications of a stroke at 63 years of age. He had chronic hypertension. He also had many café au lait spots and bumps.
Physical Exam

- Blood pressure: 130/90
- He has 6 fleshy soft lesions on his abdomen and lower extremities.
- There are >20 café au lait spots on his trunk, upper and lower extremities.
- There is freckling in the inguinal and axillary regions.

Neurofibromatosis Type I

- Occurs in 1/3000 individuals
- Autosomal Dominant inheritance
- Diagnosis: 2 of the following:
  - Family history NF1
  - >6 café au lait spots
  - 2 or more Neurofibromas
  - Lisch nodules
  - Optic gliomas
  - Angiofibromas
  - Axillary and/or inguinal freckling

Café Au Lait Spots

- >6 in number
  - Post-pubertal: >1.5 cm
  - Pre-pubertal: >0.5 cm
  - First noted birth-infancy
Freckling

- Axillary or inguinal Freckling
- 85% of patients exhibit this feature by 10 years of age.

Neurofibromas

- Soft, fleshy growth
- Superficial or deep
- Pre-adolescence

- Spindle-shaped cells
- Collagen, nerves

Optic Glioma

- Most common CNS tumor
- 15% incidence when all patients are imaged
- One third of patients with glioma develop:
  - Decreased visual acuity
  - Proptosis
  - Strabismus
  - Headaches
  - Nausea
Lisch Nodules

- Iris hamartomas
- Seen usually on slit lamp exam
- 25% age 5, 50% age 10, 95% age 20

Orthopedic Signs in NF

- Osseous defect of the fibula can be one of the first signs during infancy.

Hypertension

- Common in patients with NF1
- Can develop at any age.
- Most cases are essential
- Other causes of HTN include renal artery stenosis and coarctation of aorta.

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Management of NF1

- Yearly ophthalmologic exams
- Close blood pressure monitoring
- Removal of Neurofibromas if they are in areas causing irritation.

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Tuberous Sclerosis

- Café au lait spots noted in some
- Hypopigmented lesions seen on woods lamp/Shagreen patch
- Adenoma sebaceum
- Facial angiofibroma
- Periungual fibromas
- Retinal hamartomas
- Cortical tubers/subependymal astrocytoma
- Cerebral shagreenoma (in prenatal period/infancy)
- Autosomal dominant
- TSC1 and TSC2 genes

* Ash leaf spots, 90%, present at birth/infancy
Noonan Syndrome

- Common disorder occurring in 1/1000 individuals
- Clinical Characteristics
  - Short stature
  - Hypertelorism
  - Long and posteriorly rotated ears
  - Shield chest
  - Pectus excavatum
  - Pulmonary stenosis
  - Cryptorchidism
  - Some have multiple café au lait spots
- Inheritance: Autosomal Dominant
- Mutation in the PTPN11 gene identified in 50% of patients.
- SOS1 (10-15%), RAF1 (3-8%), KRAS (5%)
A 22 year old female has a father who died from an aortic dissection. There was concern he had Marfan syndrome and a mutation of the FBN1 gene was identified in the father. The patient was found to have the same change to the FBN1 gene identified in her father. Which of the following study is recommended?

A. Renal Ultrasound
B. Head CT
C. Audiology exam
D. Echocardiogram
E. Pulmonary function test

Clinical Presentation

A 17 year old female presents to clinic for a sports physical.
- She is an A/B student in school.
- She is on the basketball team.
- She dislocated her shoulder a year ago and continues to have pain.
Family History

- Patient B is of mixed Caucasian descent.
- She has 2 brothers ages 15 and 21.
- Her mother is 52, in good health. She is 5'2" tall.
- Her father died 1 year ago at age 51 from an MI. The fast repelling chest pain, paramedics were unable to resuscitate him. He was 6'3" tall.
- Her father has 1 living brother. He has another brother who died at age 35 from an aortic dissection.
- Patients paternal grandmother is 82 and alive, paternal grandfather died at age 52 of an apparent MI.
- Her mother is an only child.

Physical Exam

- Height 170cm (>95%). Wing span 188cm
- Weight 48kg (10%) 
- Long face, high arched palate
- Cardiovascular S1S2 with an ejection murmur
- Chest wall exhibits a pectus excavatum
- Scoliosis
- Extremities show arachnodactyly, increased flexibility + Steinberg thumb sign, + wrist sign
- Pes planus (flat feet)

Review of Systems

- She has worn glasses since 3rd grade for myopia.
- In addition to her shoulder dislocation, she also had a bad ankle sprain 2 years ago.
- She was diagnosed with scoliosis at age 12. The curve is at 20°.
Clinical Diagnosis of Marfan Syndrome

- Family history
- Skeletal/Systemic
- Cardiovascular
- Ocular

Systemic Features of Marfan syndrome

- To fulfill criteria an individual needs to have 7 systemic “points”
- Flat arch (pes planus) (1pt)
- Steinberg thumb sign and wrist sign (3pt)
- Either Steinberg thumb sign or wrist sign (1pt)

Systemic Features of Marfan Syndrome

- Chest wall deformities including pectus excavatum (1pt) and pectus carinatum (pigeon chest) (2pt)
- Spontaneous Pneumothorax (2pt)
- Scoliosis greater than 20 degrees (2pt)
Systemic Features of Marfan Syndrome

- The lower body segment is greater than the upper body (1pt)
- The wing span is greater than the height (1pt)
- Striae (1pt)
- Myopia (1pt)
- Mitral Valve prolapse (1pt)
- Facial features including high arched palate, long face, crowding of the teeth (1pt)

Ophthalmologic Features of Marfan Syndrome

- Ectopia Lentis (upward)
- Flat cornea
- Elongated globe
- Myopia (systemic) (1pt)

Cardiovascular Features of Marfan Syndrome

- Dilatation of ascending aorta (Z score > 2)
- Aortic dissection
- Mitral valve prolapse (systemic feature) (1pt)
Family History

- Marfan Syndrome is inherited in an autosomal dominant fashion.
- Approximately 60% of individuals with Marfan syndrome have a family history of the disorder.
- If an individual has Marfan syndrome there is a 50% risk they will pass the abnormal fibrillin gene to their offspring.

Laboratory Diagnosis of Marfan Syndrome

Marfan Syndrome is caused by an abnormality in Fibrillin. Fibrillin is a component of connective tissue providing elasticity. Mutation analysis of Fibrillin gene (FBN1) identifies pathogenic change in the gene in 97% of patients who fulfill the clinical diagnosis for Marfan Syndrome.

New Ghent Criteria: Without Family History of Marfan Syndrome

- Ao(Z>2) and Ectopia lentis
- Ao(Z>2) and FBN1
- Ao(Z>2) and Systemic features (7+pts)
- Ectopia lentis and FBN1
New Ghent Criteria: In the presence of Family History

- Ectopia lentis
- Systemic features (≥ 7 pts)
- Ao/Z>2 over age 20 and >3 below 20
- Familial Fibrillin gene mutation (FBN1)

Echocardiogram

- Patient is found to have a dilated aortic root.

Diagnosis of patient B

- The patient has 9 points of the systemic features including scoliosis (2pt), pectus excavatum (1pt), wing span>ht (1pt), pes planus (1pt), positive Steinberg thumb and wrist sign (3pt), myopia (1pt)
- Dilated aortic root (Z score >2)
- Systemic features, cardiovascular system with probable family history.
Genetic Counseling for Marfan Syndrome

- Patients with Marfan Syndrome have a 50% risk of passing it onto their children.
- The complications of this disorder vary among family members.

DNA Fibrillin Analysis

- An identifiable mutation of the FBN1 gene is found in 97% of patients who fulfill the clinical diagnosis.
- DNA analysis can be used to confirm the diagnosis in a patient who does not fulfill diagnosis based on clinical features and it can also be used to identify other affected family members.
- Over time we may realize different severity of phenotypes with differing gene changes.

Management for Marfan Syndrome

- Annual Eye examination
- Close Cardiology Follow up
- Medications used to lower blood pressure including B-blockers
- Limitation of sports participation if aortic root is enlarged
- Avoidance of weight lifting and scuba diving
A 22 year old female has a father who died from an aortic dissection. There was concern he had Marfan syndrome and a mutation of the FBN1 gene was identified in the father. The patient was found to have the same change to the FBN1 gene identified in her father. Which of the following study is recommended?

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CONNECTIVE TISSUE DISORDERS SIMILAR CHARACTERISTICS TO MARFAN SYNDROME

Clinical features include cerebral, thoracic and abdominal arterial aneurysms and/or dissections.

- Skeletal features include
  - pectus deformities
  - scoliosis
  - joint laxity
  - arachnodactyly
  - bifid uvula/cleft palate
  - velvety translucent skin

Risk of aortic rupture during pregnancy.

Mutations in TGFBR1/2 are identified in over 90% of patients who fulfill the clinical diagnosis.
Ehlers-Danlos Syndrome

- **Ehlers Danlos Type I** is characterized by extreme flexibility.
- **Clinical Characteristics**
  - Recurrent joint dislocations
  - Periodic joint effusion related to trauma
  - Genu varum/valgum or tonguing on nose
  - Ductal margin and excess skin on knees
  - Risk of aortic root dilatation
- **Gene:** COL5A1 and COL5A2
- **Ehlers Danlos type IV** can present with aortic dissection.
  - **Gene:** COL3A1
  - Risk of aortic dissection during pregnancy

PATIENT C

- A 5 year old male is having increasing frequency of toe walking. He has difficulty going up stairs. The creatine kinase was measured at 22,000 (nl 0-50). Which is the most likely diagnosis?
  - A. Down syndrome
  - B. Myotonic Dystrophy
  - C. Duchenne Muscular Dystrophy
  - D. Fragile X syndrome
  - E. Pompe disease
Patient C

3 year old presents to clinic with the following complaints:
- Delayed walking
- Toe walking
- Frequent complaints of leg pains
- Calf hypertrophy
- Awkward gait

Gower Sign

Family History

- Patient has a 5 year old sister, healthy
- His mother is 31
- The mother has 2 sisters
- His father is 33
- He has 2 brothers
- No one else in the family have similar problems.
Physical Exam

- Muscle weakness in both upper and lower extremities.
- Proximal weakness greater than distal weakness.
- Calf hypertrophy

THE CREATINE KINASE (CK) IS 20,000

Duchenne’s Muscular Dystrophy

- Frequency 1/5000 males
- Inheritance X-linked Recessive
- Clinical features include
  - Progressive muscle weakness
  - Calf hypertrophy
  - Toe walking
  - Lordosis
- Patients usually wheelchair bound by age 16.
- Death in late teens/early 20’s secondary to heart failure (dilated cardiomyopathy)
**DYSTROPHINOPTHIES**

- Dystrophin is a protein important in the complex that connects the action of a muscle fiber to the surrounding extracellular matrix.
- This complex is important in the movement of both skeletal muscles as well as the cardiac muscles.

**DYSTROPHIN GENE**

- Dystrophin gene is the largest known human gene, it has 79 exons/coding regions.
- The DMD gene is located on the short arm of the X chromosome (Xp22.1).
- Small deletions and point mutations can result in protein production but less functional (Becker MD).
- Becker MD is also a result of a change in this gene.

**Dystrophin**

- When the membrane does not have structural support from the cytoskeleton the membrane rips every time the muscle cells contract.
- Creatine kinase migrates from the inside of the cell to the outside.
- Elevated CK in the blood stream is a sign of muscle disease, it also depletes the muscle cells of energy.
- Ca migrates into the cell. When Ca combines with proteases, they become active and break down muscle cells.
- Over time, the muscle cells are taken over by fat cells, this results in calves hypertrophy.
Management

- Physical Therapy
- Steroid injections into the muscle
- Cardiac medications to improve function
- Exon skipping of the dystrophin gene to produce attenuated dystrophin protein

Exon Skipping

- Approximately 80% of patients with DMD have involvement in exon 51.
- PmO charged analogs bind to mRNA to hinder splicing between exons 48 and 52.
- This causes exon 51 to be skipped and can lead to restoration of the reading frame.
- While the dystrophin is shorter than normal, it will have some function (like BMD).
- The medication is given by injection on a weekly basis and has shown improvement in muscle function.

A 5-year-old male is having increasing frequency of toe walking. He has difficulty going up stairs. On exam he has proximal hypotonia. The creatine kinase was measured at 22,000 (nl 0-50). Which is the most likely diagnosis?

- A. Down syndrome
- B. Myotonic Dystrophy
- C. Duchenne Muscular Dystrophy
- D. Fragile X syndrome
- E. Pompe disease
Down Syndrome

Caused by an additional copy of chromosome 21

- Clinical characteristics
  - Congenital Hypotonia
  - Flat face
  - Simean crease
  - Clinodactyly (incurving 5th finger)
  - Congenital anomalies
    - Congenital Heart defect
    - Quadriplegia
    - Hip scarring disease

- Cognitive issues
  - Developmental delay
  - Autism (5-10% of patients)
  - Alzheimer’s in the 50’s

Myotonic Dystrophy

- Gene on chromosome 19
- CK is not elevated
- Triple repeats of CTG
  - Up to 50 repeats is normal
  - Adult onset disease: 50-200 repeats
  - Congenital >6000 repeats
- Clinical characteristics
  - Muscle weakness
  - Myotonia
  - Difficulty releasing a grip
  - Cataracts
  - Early frontal balding
  - Expressionless face

Fragile X

- Most common single gene cause of Autism
- Seen in males and females, more severe in males
- Triple repeat CGG repeat expansion on the 5’ end of the gene
- Clinical characteristics
  - Large ears
  - Long face
  - Joint hyperextensibility
  - Hypotonia
  - Enlarged testes (post pubertal)
Pompe Disease

- Clinical Characteristics
  - Congenital hypotonia (adult form presents later)
  - Cardiomyopathy
  - Respiratory insufficiency
  - Elevated CK (200-1000)
  - Adult form can present later
  - Autosomal Recessive, GAA gene

  - This gene is responsible to metabolizing glycogen in the Lysosomes

PATIENT D

- A 3 month old female has macroglossia, hemihypertrophy and glabellar hemangioma. Which of the following is the patient at greatest risk for developing?
  - A. Fracture
  - B. Anemia
  - C. Colon cancer
  - D. Aortic root dilatation
  - E. Wilms tumor
Patient D

- A 3 month old presents to clinic
- She is at the 95% for height and weight
- Her parents are concerned that her tongue often protrudes out of her mouth.

Birth History

- Born full term by C-section for failure to progress.
- Birth weight 9#2oz
- She was in the NICU for 2 days because of hypoglycemia

Family History

- First child, conceived by IVF
- The mother has 2 brothers and one sister.
- The father is an only child
- The grandparents are alive/healthy
Physical Exam

- Weight: 344 g (95%)
- Length: 47 cm (95%)
- HC: 38 cm (50%)
- Glabellar hemangioma
- Tongue protruding
- Right ear measures 4 cm, left 5 cm, creases on both ears
- Cardiac exam is normal
- Abdomen: smooth abdomen, umbilical hernia present
- Extremities: normal distribution, normal tone, normal reflexes
- Right foot measures 10 cm, left measures 12 cm
- There is a 1 cm leg length discrepancy with the left leg longer than the right.

Symptoms

- Neonatal hypoglycemia
- Macrosomia (large baby)
- Asymmetry/hemi hypertrophy
- Macroglossia
- Umbilical hernia
- Beckwith-Wiedemann (BWS)
  - Increased birth weight
  - Hypoglycemia (neonatal)
  - Glabellar hemangioma
  - Hypocalcemia
  - Umbilical hernia/omphalocele
  - Anterior ear creases
Beckwith-Wiedemann Syndrome

- Macroglossia
- Wilms Tumor
- Hepatoblastoma
- Omphalocele
- Organomegaly
- Hemihiperplasia

Genetics of Beckwith-Wiedemann Syndrome

- There are 3 genes associated with BWS. They are all involved in growth and development. They are located next to each other on chromosome 11, KCNQ1 (C2) and CDKN1C (C1) and IGF2 (C1).
- In most individuals, the KCNQ1 gene is only active from the father, the mother's copy is "methylated". If the mother's copy is not methylated, there is overexpression/overgrowth (50% of cases).
- In most individuals, the IGF2 gene is only active when inherited from the mother. If the IGF2 is methylated from the mother, it can affect growth (5%)
- Both regions of chromosome 11 are donated from the father (UPD). (Both copies of KCNQ1 are active and both copies of IGF2 are methylated)
- Mutation of the maternal copy of the CDKN1C gene (20%)

All of these changes can lead to overgrowth.

Beckwith-Wiedemann (BWS)

- Incidence: 1/15,000
- Increased incidence of BWS in infants conceived by IVF because of abnormalities in methylation.
- BWS is associated with an increased risk for Wilms tumor (kidney tumor) Approximately 5% of patients with BWS will develop a Wilms tumor
- Increased risk for Hepatoblastoma (low risk but greater than the general population)
- Anticipatory Guidance:
  - Renal US Q3mo until age 8
  - AFP every 3 months until age 3.
A 2 month old female has macroglossia, hemihypertrophy and glabellar hemangioma. Which of the following is the patient at greatest risk to develop?

A. Fracture  
B. Anemia  
C. Colon cancer  
D. Aortic root dilatation  
E. Wilms tumor

PATIENT E

A 6 month old male presents with failure to thrive. His height, weight and head circumference are below the 5%. He was born full term with a birth weight of 4#5oz. He had hypospadias at birth and a VSD. On exam he has 2/3 syndactyly of the toes bilaterally. He is noted to have elevated 7-dihydrocholesterol. What is the most likely diagnosis?

A. Fetal Alcohol syndrome  
B. Prader Willi syndrome  
C. Smith Lemli Opitz  
D. Pompe disease
**Smith Lemli Syndrome**

- Inherited in an autosomal recessive fashion
- Caused by a mutation of the DHCR7 gene located on chromosome 11
- The enzyme produced by the DHCR7 gene converts 7-dehydrocholesterol to cholesterol
- When the DHCR7 gene does not function, the cholesterol is low and 7-dehydrocholesterol is elevated (7DHC)

**Clinical Characteristics of Smith Lemli Opitz (SLO)**

- Microcephaly
- Short nasal root, anteverted nares
- Ptosis
- Low set ears
- 2/3 Syndactyly of hands and feet and polydactyly
- Hypospadias in males, small labia in females, ambiguous genitalia
- Congenital heart defects including ASD, VSD and AV canal

**Management**

- NG feeding as an infant
- Cholesterol supplementation
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Fetal Alcohol Syndrome

- Failure to thrive, below 5% for height, weight and head circumference
- Prenatal alcohol exposure
- Clinical Characteristics
  - Microcephaly
  - Low birth weight
  - Failure to thrive (FTT)
  - Long smooth philtrum
  - Thin upper lip
  - Hearing loss
  - Congenital heart defects

Dysmorphic features

- Short Palpebral fissure length, hypertelorism
- Long philtrum
- Thin upper lip
Diagnosis of FAS
- Prenatal Alcohol Exposure
- Dysmorphic features
- Growth deficiency
- Cognitive delays

Fetal Alcohol Syndrome (FAS)
- One of the most common causes of mental retardation.
- 1/1000 live births
- 1/100 live borns are affected with Fetal Alcohol Effects (FAE)

Prader-Willi Syndrome
- Infancy
  - Severe hypotonia
  - Failure to thrive (postnatal, usually have a normal birth weight)
- Older children
  - Obesity
  - Hypotonia
  - Small hands and feet
  - Up slanting palpebral fissures
  - Developmental Delays IQ 60-70
Prader-Willi Syndrome

- Only the paternal copy of the SNP gene on 15q11 is active (the maternal copies is methylated off).
- Approximately 70% of cases are caused by a paternal deletion of chromosome 15q11.2 (microdeletion).
- 30% are a result of uniparental disomy.

USMLE TYPE QUESTION

- A 12-year old boy has a particular genetic disease. His mother is a carrier of the mutated gene, but his father is not clinically affected and is not a carrier. The patient has four siblings: a sister and brother who are not clinically affected and not carriers, a sister who is a carrier but not affected and a brother who is clinically affected. This inheritance pattern is consistent with which of the following diseases?
  A. Alpha1-antiprotein deficiency
  B. Cystic Fibrosis
  C. Duchenne Muscular dystrophy
  D. Phenylketonuria
  E. Tay-Sachs

Conclusion

- Understanding the presentation of common genetic disorders will help to anticipate problems (cancer in BWS, aortic dissection in Marfan syndrome).
- Diagnosis of an increasing number of genetic disorders may help in early treatment (enzyme replacement) and better outcome.
- When reading the question pay attention to unusual information such as “urine smells”, unusual lab values, family history information.