Genetics of Primary Pain Disorders

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Objectives:

1. Define pediatric pain disorders and place them into the larger framework of inborn errors of development and metabolism.
2. Describe the clinical characteristics of Hereditary Sensory and Autonomic Neuropathies (HSAN)
3. Present an approach to genetic evaluation of patients and families

I. Inborn Errors of Development (IED) and Metabolism (IEM)

Development. These are genetic disorders that are characterized by failure of normal organogenesis or tissue histogenesis beginning in early development and continuing during later life. IED result from mutations in pathways that control cellular differentiation, proliferation, movement, and cell-cell interactions.

Metabolism. These are genetic disorders characterized by the failure of specific pathways of intermediary metabolism. IEM result in tissue and organ injury due to accumulation of toxic products, energy depletion, or failure of production of needed anabolic intermediates.

II. Hereditary Sensory & Autonomic Neuropathies (HSAN) – Differential Diagnosis

Amyloidosis
An-α-lipoproteinemia (Tangier's)
α-galactosidase (Fabry's)

HSAN Type I: Small fiber loss
HSAN Type II: Large & Small fiber loss
HSAN Type III: Riley-Day Syndrome
HSAN Type IV: Congenital sensory neuropathy with anhidrosis
HSAN Type V: Congenital absence of pain sensation without anhidrosis

Cold-Induced Sweating Syndrome
Hereditary ataxia with thermoanalgesia & loss of fungiform papillae
Navajo neuropathy with arthropathy
Hereditary sensory neuropathy + Spastic paraparesis (Cavanagh's variant)
Biemond congenital anaesthesia
Dominant ataxic neuropathy

III. Congenital insensitivity to pain with anhidrosis (CIPA, HSAN 4)

Clinical Features

- Congenital insensitivity to pain
- Decreased corneal sensitivity & reflexes
- Reduced pain sensation, temperature & visceral
- Idiopathic; Episodic fevers
- Episodic hyperpnea
- Absent sweating
- Skin blotching
- Mental retardation
- Self mutilation: Joint deformities of knees & ankles; Tip of tongue; Lips
- Finger nail dystrophy
- Slow wound healing

Laboratory

- No histamine axon flare response
- No tearing with mecholyl
- Absent sympathetic skin responses
- Nerve conduction velocities normal range
- Anemia (79%)

Pathology

- Small myelinated & unmyelinated axons: 0% to 5% of normal
- Large myelinated axons; Mildly reduced
- Dorsal root ganglia: Small sensory neurons absent
- Absence of innervation of eccrine glands
- Reduced innervation of the skin

Molecular Genetics
- Chromosome 1q21-q22;
- Recessive inheritance
- Gene mutations in **T**RKA/ NGF receptor
  - High prevalence in Israeli-Bedouins due to 1926-ins-T mutation
  - Mutations in same gene associated with familial medullary thyroid carcinoma

Physiology:
- survival activity on nervous tissue
- secreted by cells in the target field protect the neurons from apoptosis
- regulation of neuronal plasticity and in
- regulating the number of neural progenitor cells

IV. Hereditary Sensory Neuropathy I (HSAN I; HSN I)

Clinical
- 2nd decade or later; Average 25 years
- Distal > proximal; Symmetric; Legs > Arms sensory, autonomic & reflex loss
- Pain & Temperature (Small fiber); Large fiber loss
- Paresthesias are Rare; Lancinating pains in some kindreds; Burning pain in some
- Charcot's joints (Neurogenic osteoarthropathy)
- Succession of exacerbations
- Feet, Severe mutilation & shortening
- Distal demineralization; Metatarsal tapering (Licked candy-stick)
- Weakness
- Sensorineural deafness: Variably present
- Blistering; Edema & discoloration of foot; Chronic ulcers; Painless injuries

Laboratory
- Electrophysiology: Loss of C > Aδ & Aα axons
- Immune: Increased Synthesis of IgA

Pathology
- loss of dorsal root ganglion cells & later motor neurons
- predominant loss of small myelinated & unmyelinated axons
- loss of ganglion cells in the sacral and lumbar dorsal root ganglia
- proliferation of subcapsular dendrites
- clear hyalin bodies in the involved ganglia
- no CNS changes

Molecular Genetics
Serine palmitoyltransferase, long-chain base subunit 1 (SPTLC1)
Chromosome 9q22.1-q22.3;
Dominant inheritance
Serine palmitoyltransferase (SPT) enzyme: Sphingolipid biosynthesis catalyzes pyridoxal-5'-phosphate-dependent condensation of L-serine & palmitoyl-CoA to 3-oxosphinganine

V. Riley-Day Syndrome (HSAN 3)

Clinical
hypothermia, vomiting crises in newborn
absent fungiform tongue papillae
pain & temperature insensitivity; large fiber modalities relatively spared
absent deep tendon reflexes
irritability, fever, fainting
postural hypotension with no compensatory tachycardia
hypertensive crises
skin blotching
normal sympathetic skin responses
GI dysfunction: GE reflux; vomiting crises
scoliosis
abnormal responses to hypoxic & hypercarbic states; recurrent pneumonias
finger nail dystrophy
taste: reduced
psychiatric syndromes
usually fatal - death in 50% < 30 years

Pathology
marked progressive reduction of unmyelinated axons: 5% to 15% of normal
loss of autonomic neurons
large axons relatively spared - 65% to 100%

Molecular Genetics
Inhibitor of k light polypeptide gene enhancer in B cells, kinase complex-associated protein (IKBKAP)
Chromosome 9q31
Recessive inheritance
T to C transition in base pair 6 in donor splice site of intron 20 (2507+6T-C)
Major haplotype: Present in 99.5% of disease alleles
Common ancestral haplotype: Founder effect
Carrier frequency in Ashkenazi-Jewish population: 1/36
Mutation effect: May cause skipping of exon 20; Wild type message expressed in tissue-specific manner
All patients heterozygous for major haplotype

VI. Other Syndromes

Congential insensitivity to pain without anhidrosis (HSAN V)

- Congenital loss of pain sensation in the extremities
- Normal large fiber sensation, strength & tendon reflexes
- Absent small myelinated A-delta fibers

Hereditary ataxia with thermoanalgesia & loss of fungiform papillae
Autosomal Dominant
Onset: 5th decade
Impaired pain & temperature sensation
Loss of myelinated > unmyelinated axons
Ataxia
Absent Fungiform papillae of tongue
Reduced lacrimation, taste, temperature control (fevers)
Constipation/diarrhea; Bladder dysfunction; Vasomotor instability
Emotional instability; Hearing loss

Neuropathy, congenital sensory, with neurotrophic keratitis - Navajo neuropathy
autosomal recessive, mean age of death 10 years
anesthesia (leading to corneal ulceration, painless fractures
severe weakness, absent or markedly decreased deep tendon reflexes
normal IQ
systemic infections
poor weight gain
sexual infantilism
hepatomegaly, persistent neonatal jaundice, Reye-like syndrome, macronodular cirrhosis

Biemond Congenital and Familial Analgesia
loss of pain sensation; diminished touch and temperature sense
absent tendon reflexes
Abnormal neural development: posterior root ganglia; posterior roots; posterior horns of the spinal gray matter; posterior columns; spinothalamic tracts could not be demonstrated

Hereditary sensory neuropathy + Spastic paraparesis (Cavanagh's variant)
slowly progressive spastic gait
marked loss of pain and temperature sensations; mutilating acropathy
symmetric, axonal, predominantly sensory neuropathy
Sural nerve biopsy predominant involvement of unmyelinated and global loss of myelinated fibers, particularly larger ones

Bone pain, periodic (112270)
Single kindred - 33 persons in 7 generations were considered affected
periodic arthralgia; pain located in the shafts of the long bones

Pain, Submandibular, Ocular and Rectal, With Flushing
excruciating pain of the submandibular, ocular and rectal areas with flushing of the surrounding skin
Autosomal dominant inheritance with variable penetrance
Submandibular and ocular pain is a more consistent feature than rectal pain

Acromelalgia, Hereditary (Restless Legs)*102300
paresthesia when first going to bed or sitting still for a time
affected person cannot resist fidgeting with his or her feet
Autosomal dominant inheritance – multiple pedigrees
myoclonic jerks in 10 of 18 affected persons.
30-year age-at-onset difference between generations

VII. Erythromelalgia

Pain

- Early: Distal extremities; Legs > Arms; Relative sparing of toes
- Bilateral; Symmetric
- May spread to hands, earlobes & nose tip
- Burning
- Dysesthesias with touch
- Environmental factors
  Exacerbated by Heat; Standing; Exercise
  Relief by Cold; Elevation of extremity
- Associated with warmth & flushing of extremity; Red; warm skin
- Episodic
- Severity may increase with age
- Area involved may increase

Familial erythromelalgia

- Chromosome 2q31-32; Dominant
- Onset: Childhood & adolescence

Treatment

- Aspirin - rapid (1 hour) short-lived improvement
- Pain control: Capsaicin + Systemic analgesia
- Cooling of affected limbs
- ? Epidural anesthesia

Pathophysiology

- ? Hyperactive axon reflex in C-nociceptor fibers
- Skin pathology: Nonspecific; ? Reduction in autonomic plexi

IX. Reflex Sympathetic Dystrophy (Complex regional pain syndrome)

Clinical

- Female:Male 2:1
- Age: Mean 50 years; Range 15 to 80 years
- Associated features
- History of chronic pain (40%): Back; Headache
- Precipitating events
- Limb fractures
- General surgery
- Soft tissue injury
- Drugs
- Phenobarbital; Phenytoin; Isoniazid; Cyclosporin
- Medical conditions
- Diabetes mellitus; HyperThyroid; HyperParathyroid; Type IV hyperlipidemia
- Clincial Features
- Onset: Weeks after precipitating event
- Location
- Distal extremity
- Hands > Feet; Knees
- Asymmetric or Unilateral most commonly

Burning; Continuous Pain

- Allodynia & Hyperpathy
- Exacerbated by movement and cutaneous stimulation stress & temperature change
- Cold pain more common with nerve lesions
- Sensory loss Glove or Stocking; pain and touch

Autonomic

- Increased skin temperature
- Hyperhidrosis
- Edema
- Skin color change

Motor disorders

- Sense of weakness with complex motor tasks (79%)
- Difficulty initiating movements
- Limited range of motion

Involuntary movements

- Tremor (48%)
- Irregular myoclonic jerks, dystonia or muscle spasm (30%)
- Tendon reflexes: Increased affected side 46%

X. Background Reading

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