Inborn Errors of Metabolism

by Kristina Burke, MD, and Erin Adams, MD

DISORDER	DEFECT	SKIN FINDINGS	OTHER
Alkaptonuria (Endogenous ochronosis) **AR**	Homogentistic acid oxidase Disorder of phenylalanine and tyrosine metabolism. Homogentistic acid accumulates	Blue-grey pigmentation of nose, ears, axillae, genitalia and cartilage. Blue sclera (Osler's sign), dark urine (pH >7), black cerumen	- Large joint arthropathy - Intervertebral disc calcification - Mitral/aortic valve disease - Nephrolithiasis
Fabry's disease (Angiokeratoma Corporis Diffusum) **XLR** A lysosomal storage disease	α-galactosidase A (glycolipids accumulate in skin, heart, kidneys)	Angiokeratomas (esp lower extremities, scrotum, penis, and lower trunk), whorl-like corneal opacities, edema, hypohldrosis	- Renal failure, cardiovascular events, strokes - Acroparesthesias and painful crises - Maltese cross in urine - Enzyme replacement available
Fucosidosis **AR** A lysosomal storage disease	α-L- fucosidase	Angiokeratomas, coarse features, facial dysmorphism	- Mental retardation (MR), neurologic deterioration
Gaucher disease **AR** A lysosomal storage disease	Acid-β-glucosidase (glucocerebrosidase) Leads to accumulation of glucocerebroside in histiocytes (Gaucher's cells)	Type 1: diffuse hyperpigmentation, petechiae, pingueculae of sclera Type 2: congenital ichthyosis, collodian baby	ALL: hepatosplenomegaly (HSM) - Type I: Adult type, Ashkenazi Jews, no CNS involvement - Type 2: infantile, rapid neuro deterioration, aspiration pneumonia - Type 3: juvenile chronic neuropathic
Phenylketonuria **AR**	Phenylalanine hydroxylase (Phenylalanine not oxidized to tyrosine)	Pigmentary dilution of skin, hair, eyes (fair complexion, blond hair, blue eyes), pseudoscleroderma, eczematous dermatitis	- MR, seizures - Phenylpyruvic acid in urine (musty odor) - Screened for at birth - Dietary restriction
Tyrosinemia II (Richner-Hanhart) **AR**	Tyrosine aminotransferase (hepatic) TAT gene	Painful palmoplantar keratoderma	- Herpetiform keratitis, blindness - MR - Corneal ulcers
Homocystinuria **AR**	Cystathionine β-synthase	Fair complexion, malar flush, livedo reticularis, leg ulcers Sparse, fine hair Marfinoid habitus	- Thromboembolic events (50% by 30yo) = common cause of death - Ectopia lentis (downward) - Osteoporosis - MR, developmental delay
Niemann-Pick disease **AR** A lysosomal storage disease	Type A and B: Sphingomyelinase (SMPD1) Type C: NPC1 and 2	Type A and B: ochre to brownish-yellow discoloration of skin, papular lesions face and upper extremities, xanthomas	Type A: severe, CNS deterioration, HSM, failure to thrive Type B: spares CNS, survival to adulthood Type C: childhood, HSM, developmental delay, psychomotor deterioration
Trimethylaminuria "Fish odor syndrome"	Mutation of flavin-containing monooxygenase type 3 (FMO3) gene	Skin, urine, and sweat smell like "rotting fish"	- Smell due to accumulation of trimethylamine - Avoid choline in diet
Lesch-Nyhan (juvenile gout) **XLR**	HPRT1 gene leading to hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency	Loss of tissue around mouth and fingers (due to self-mutilation) Tophaceous deposits (hyperuricemia)	- MR, choreoathoid movements, self-mutilation - Orange crystals in diaper
Wilson's disease (Hepatolenticular degeneration) **AR**	Defect in ATP7B gene (hepatic copper transporting ATPase)	Blue lunulae, Kayser-Fleischer rings (copper deposition in Descemet's membrane), greenish discoloration of face, neck and genitalia, pretibial hyperpigmentation	- HSM, cardiomyopathy, renal tubular acidosis - Progressive neurologic dysfunction (dysrthria, ataxia, dementia) - Lab: low ceruloplasmin - Tx: penicillamine, trientine, zinc supplement
Hartnup disease **AR**	SLC6A19 gene (neutral amino acid transporter)	Pellegra-like dermatitis (photosensitive eruption on face, arms, neck, legs)	- Cerebellar ataxia, MR - Tends to improve with age - Defect in tryptophan transport

Kristina Burke, MD, is a third year resident at Walter Reed National Military Medical Center in Bethesda, Md.

Erin Adams, MD, is a staff dermatologist at Walter Reed National Military Medical Center and also academic staff for the National Capital Consortium Dermatology Residency Program.

Inborn Errors of Metabolism (continued)

by Dr. Burke, MD and Dr. Adams, MD

DISORDER	DEFECT	SKIN FINDINGS	OTHER
Prolidase deficiency	Deficiency of the enzyme prolidase	Skin fragility, lower extremity ulceration, telangiectasias, poliosis	- Mental deficiency, recurrent infections, syndromic facies
Citrullinemia	Type 1: argininosuccinic acid synthetase (ASS1 gene) Type 2: SLC25A13 gene	Resembles zinc deficiency Erythematous, erosive, scaling patches periorally, lower abdomen, and diaper area	- Clears with arginine supplementation
Farber disease A lysosomal storage disease	Ceramidase deficiency	Periarticular swelling, rubbery SQ nodules	- Onset first month of life, death by age 2 - Weak, hoarse cry; pulmonary failure, MR
Adrenoleukodystrophy (Schilder's disease) X-linked	ALD gene	Hyperpigmentation, mild ichthyosis, sparse hair with trichorrhexis nodosa-like features	- Progressive demyelination of cerebral white matter
CADASIL Cerebral autosomal dominant arteriopathy w/ subcortical infarcts and leukoencephalopathy	NOTCH 3 gene	Findings on skin biopsy (eosinophilic granular material in arterial walls)	- Depression, migraine headaches - Multiple cerebral infarcts leading to early dementia - Most common hereditary stroke disorder
Lafora disease (Lafora progressive myoclonic epilepsy)	EPM2A- encoding laforin EMP2B – encodes a ubiquitin ligase	Few – rarely see papulonodular lesions over ears, plaques on arms	- Progressive epilepsy syndrome - Dementia and ataxia - Best site to biopsy = axilla (Lafora bodies around eccrine ducts)
Alagille syndrome **AD**	JAG 1	-Xanthomas, jaundice -Unusual facies	- Congenital intrahepatic biliary hypoplasia w/ cholestasis and pruritus. - Hyperlipidemia - Butterfly-shaped vertebra
Sitosterolemia **AR** "phytosterolemia"	ABCG5 (encoding sterolin-1) or ABCG8 (encoding sterolin-2)	Tuberous and tendinous xanthomas during the first decade of life	- Elevated plasma levels of plant sterols - Arthritis, premature vascular disease, high risk of fatal cardiac events during teenage years
Hurler syndrome **AR** "gargoylism" A lysosomal storage disease	Deficiency of α-L-iduronidase	Diffuse fine lanugo hair, extensive blue pigmentation Facial dysmorphism, large tongue, thick lips	- MR, HSM, corneal opacities, umbilical hernia - Dental abnormalities, persistent rhinitis
Hunter syndrome **XLR** A lysosomal storage disease	Deficiency of iduronate-2-sulfatase	Skin-colored pebbly lesions of the upper back, neck, chest, proximal extremities	- Dysotosis multiplex
Tangier Disease **AR** (Familial α-lipoprotein deficiency)	ATP-binding cassette (ABCA1) transport protein: almost complete absence of plasma HDL and massive deposition of cholesterol esters in tissues	Tonsils are yellow and enlarged. Maculopapular eruption over trunk and abdomen	- HSM, lymph node enlargement, peripheral neuropathy, corneal infiltration in adults - Premature coronary artery disease

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