Disorders of Lipid Metabolism Dr. Amar Babikir Elhussein Associate Professor of Biochemistry and Molecular Biology Disorders of Lipid Metabolism ?Importance in clinical medicine.ketones o Features: muscle weakness, cardiomyopathy o Hypoketotic hypoglycemia o Tx: carnitine, avoid fasting MCAD Deficiency o Defect: medium-chain acyl-CoA dehydrogenase o Biochemical: block in ?-oxidation o Features: hypoketotic hypoglycemia, seizures o Risk of sudden infant death o Tx: avoid fasting, IV glucose Other FA Oxidation Defects o VLCAD deficiency (long-chain) o CPT I/II deficiency (carnitine shuttle) o Features: impaired fasting tolerance o Myopathy, weakness Ketone Body Disorder: HMG-CoA Lyase Deficiency o Defect: HMG-CoA lyase o Biochemical: cannot make ketones o Features: fasting hypoglycemia, seizures o Labs: absent ketones o Tx: frequent feeding, glucose Ketone Body Utilization: SCOT Deficiency o Defect: SCOT enzyme o Biochemical: cannot utilize ketones o Features: ketoacidosis, neurologic crises o Tx: avoid fasting, supportive Succinyl-CoA:3-ketoacid CoA transferase Gaucher Disease o Defect: ?-glucocerebrosidase o Biochemical: glucocerebroside accumulation o Features: hepatosplenomegaly, bone crises o Crumpled paper macrophages o Tx: enzyme replacement Niemann-Pick Disease o Defect: sphingomyelinase o Biochemical: sphingomyelin accumulation o Features: cherry-red macula, hepatosplenomegaly o Neurodegeneration Tay-Sachs Disease o Defect: hexosaminidase A o Biochemical: GM2 ganglioside accumulation o Features: cherry-red macula, neurodegeneration o No hepatosplenomegaly Fabry Disease o Defect: ?-galactosidase A (X-linked) o Biochemical: Gb3 accumulation o Features: angiokeratomas, neuropathic pain o Renal failure o Tx: enzyme replacement Summary & Take-Home Messages o Disorders grouped by defect o Key = enzyme/protein deficiency o Labs + clinical signs -> diagnosis o Therapy: diet, drugs, enzyme replacement o Clinical importance: CAD, pancreatitis, organ failurecholesterol o Tx: diet, fibrates, omega-3 Abetalipoproteinemia o Defect: MTP mutation -> no ApoB lipoproteins o Biochemical: no chylomicrons, VLDL, LDL o Features: fat malabsorption, vitamin deficiency o Labs: absent ApoB lipoproteins o Tx: vitamins, diet *Gene encodes the microsomal triglyceride transfer protein (MTP) Tangier Disease (Hypoalphalipoproteinemia) o Defect: ABCA1 mutation o Biochemical: impaired cholesterol efflux -> low HDL o Features: orange tonsils, neuropathy o Labs: HDL severe risk o Therapeutic target = ?Key Clinical Consequences o Dyslipidemia -> atherosclerosis, CAD o TG excess -> pancreatitis o FA oxidation defects -> hypoglycemia o Lysosomal defects -> organomegaly, neurodegeneration Classification of Disorders o Hyperlipoproteinemias (I-V) o Hypolipoproteinemias o FA oxidation defects o Ketone body disorders o Lysosomal storage diseases Type I: Familial Chylomicronemia o Defect: LPL or ApoC-II deficiency o Biochemical: TG not hydrolyzed o Features: eruptive xanthomas, pancreatitis o Labs: ?TG, milky plasma o Tx: very-low-fat diet Type IIa: Familial Hypercholesterolemia o Defect: LDL receptor/ApoB mutation o Biochemical: impaired LDL clearance o Features: tendon xanthomas, arcus cornealis o Labs: ?LDL Visual Summary (Hypolipoproteinemias) o ApoB deficiency -> absent LDL/chylomicrons o ABCA1 defect -> absent HDL o LCAT defect -> abnormal HDL o Lab patterns & signs compared Carnitine Deficiency o Defect: impaired FA transport o Biochemical: ?Identify hyper/hypolipoproteinemias ?Recognize FA oxidation & ketone body disorders ?Correlate defect with clinical outcome Normal Lipid Transport (Overview) o Chylomicrons: dietary TG transport.LDL + VLDL o Tx: statins +- fibrates Type III: Familial Dysbetalipoproteinemia o Defect: ApoE2

.homozygous o Biochemical: ??Focus: lipoproteins, FA oxidation, storage diseases