Disorders of pyrimidine metabolism pdf

 Inherited disorders of purine and pyrimidine metabolism have a wide variety of clinical presentations including anemia, immunodeficiency, renal stones, convulsions, mental retardation, autism, growth retardation, and serious adverse reactions to medication.From: Reference Module in Biomedical Sciences, 2014 Key symptoms and signs of purine and pyrimidine disorders: Nephropathy/ renal failure Hematopoietic disease / immunodeficiency Developmental delay / seizures Disorders of Purine Metabolism Clinical manifestations of purine catabolism result from insolubility of uric acid. Overproduction of uric acid leads to hyperuricemia and gout. The overproduction can be severe enough to lead to death. The main purine disorder is hypoxanthine-guanine phosphoribosyltransferase deficiency; however, as described throughout this chapter there are multiple disorders leading to consequences affecting the neurologic, renal, hematologic and immune systems. Also of great importance is the fact that genes involved in both purine and pyrimidine metabolism play a critical role in drug metabolism, which is a fact that has a practical application. Renal manifestations: Familial juvenile hyperuricemic nephropathy (juvenile gout) manifests with gout, hypertension, rapid progressive renal insufficiency, renal stones and renal failure. Aldehyde oxidase and xanthine dehydrogenase deficiency (xanthinuria II) presents with urinary tract infection (UTI), nephrolithiasis and acute renal failure. Adenine phosphoribosyltransferase deficiency (2,8-di-OH-adenuria) presents with renal lithiasis, crystalluria, acute renal failure and UTIs. Lesch-Nyhan disease (LND) manifests with crystalluria and urolithiasis. Xanthine dehydrogenase deficiency (xanthinuria I): Xanthine lithiasis, acute renal failure and UTI. Hypoxanthine-guanine phosphoribosyltransferase deficiency: urolithiasis and acute renal failure. Neurologic manifestations: Adenylosuccinate lyase deficiency (adenylsuccinase deficiency) is differentiated into 1) Type I: presenting with intractable seizures, profound psychomotor retardation and autistic features, and 2) Type II: presenting with mild to moderate psychomotor retardation and contact disturbances and finally, 3) a Neonatal form: presenting with encephalopathy, hypotonia and seizures. AICAR transformylase and IMP cyclohydrolase deficiency (ATIC) manifests with neurologic deficits, patients are dysmorphic and congenitally blind. Hypoxanthine-guanine phosphoribosyltransferase deficiency manifests with choreoathetosis, spastic quadriplegia, mental/growth retardation and self mutilation when associated of the LND type. Molybdenum cofactor deficiency (combined deficiency of AO, XDH, and SO, xanthinuria-III, xanthinuria sulfituria): may present with neonatal intractable seizures, severe neurologic abnormalities, and sometimes microcephaly. Purine nucleoside phosphorylase deficiency (PNP deficiency): manifests with mental/motor retardation, ataxia and hypo or hypertonia. Xanthine dehydrogenase deficiency (Xanthinuria I): may present with mental retardation or hypotonia. Other manifestations; gout, liver failure, weakness and more: Adenylate deaminase deficiency (AMP deaminase deficiency): presents with exercise related muscular weakness, muscle cramps and myalgia. Deoxyguanosine kinase deficiency: is a mitochondrial depletion syndrome and is one of the hepatocerebral variety presenting with hepatic failure and seizures. Familial juvenile hyperuricemic nephropathy, as the name suggests, presents with juvenile gout. LND manifests with gouty arthritis. Inosine monophosphate dehydrogenase deficiency type I deficiency or IMPDHI has a main presentation of retinitis pigmentosa. Phosphoribosylpyrophosphate synthase superactivity leads to sensorineural deafness. Thiopurine methyltransferase deficiency (TPMT deficiency): presents most commonly after the administration of medications which require metabolism of azathioprine and mercaptopurine. Disorders of Pyrimidine Metabolism The inherited defects involving pyrimidine metabolism lead to nervous system, hematologic and mitochondrial disease. Most patients with this category of disease manifest with neurological and developmental problems. Hematologic and immune manifestations: Activation induced cytidine deaminase deficiency (hyper IgM syndrome type II) manifests with recurrent bacterial infections, and lymphoid hyperplasia. CTP phosphocholine cytidylyltransferase deficiency manifests with hemolytic anemia. Uridine monophosphate hydrolase deficiency (pyrimidien 5′-nucleotidase superactivity, UMPH-1 deficiency) presents with non-spherocytic hemolytic anemia, basophilic stippling and splenomegaly. Orotate phosphoribosyltransferase deficiency (OA type I) may present with megaloblastic anemia. Orotidyclic acid decarboxylase deficiency presents with immunodeficiency. Neurologic manifestations: Dihydropyrimidine deficiency (dyhydropyrimidinuria): present with a variety of neurologic symptoms including spastic quadriplegia and microcephaly. Uridine monophosphate hydrolase superactivity (UMPHS): presents with developmental delay, fits, seizures, hyperactivity. Ureidopropionase deficiency (NC-BALA amidohydrolase deficiency) has a variable presentation including hypotonia, developmental delay, seizures, and optic atrophy. Disorders of Purine and Pyrimidine Metabolism affecting Drug Metabolism Inosine triphosphate pyrophosphodydrolase deficiency (ery-ITPA deficiency): possible thiopurine drug toxicity. Thiopurine methyltransferase deficiency (TPMT deficiency): 6-Azathioprine and mercaptopurine toxicity. Dihydropyrimidinase deficiency (dihydropyrimidinuria) severe toxicity to 5-fluorouracil. Dihydropyrimidine dehydrogenase deficiency: severe toxicity to 5-fluoruracil. What other disease/condition shares some of these symptoms? Multiple systems are affected by disorders of purine and pyrimidine metabolism and as a result the differential diagnosis for these conditions is lengthy. Renal Diseases: -Nephrolithiasis Genetic Diseases: -Chromosomal aberrations -Single gene disorders Other Metabolic Diseases: -Aminoacidurias -Urea Cycle Defects -Organic Acidemias Hematologic Disease: -Leukemia -Lymphoma Immunologic Diseases: -Brutons agammaglobulimemia -Severe combined immunodeficiency disease (SCID) -Common variable immunodeficiency (CVID) What caused this disease to develop at this time? Disorders of purine and pyrimidine metabolisms may present shortly after birth with seizures, as is seen in molybenum co-factor deficiency when a patient is homozygous null for an essential enzyme. Disorders may also appear in later decades after exposure to medications reliant upon entirely intact purine/pyrimidine pathways. Such patients may be heterozygous for an essential enzyme in which case haploinsufficiency is observed. What laboratory studies should you request to help confirm the diagnosis? Laboratory studies necessary for the diagnosis of purine and pyrimidine disorders include testing of metabolites and genetic sequencing. The development of chromatographic separation techniques has played a critical role in the diagnosis of inborn errors of purine and pyrimidine metabolism. Diagnosis also relies on high performance liquid chromatography, tandem mass spectrometry and enzyme assays. Measurement of serum and urine uric acid, including quantitative measurement of urinary uric acid/′creatine ratio should be the first approach towards the detection of purine defects. Sulfite test dipstick for molybdenum cofactor deficiency, thin layer chromatography for adenylosuccinate lyase deficiency and gas chromatography-mass spectrometry should be components of baseline investigations for purine and pyrimidine disorders. Enzyme analysis, both prenatally and postnatally, is useful tool in specific diagnosis. Given the large number of new mutations arising in these disorders, measurement of enzyme activity is a more powerful test of the presence of disease-causing mutations in the relevant gene (Clarke 2006). Interpretation of all of the above testing should be discussed with a biochemical geneticist. Would imaging studies be helpful? If so, which ones? Neuro and renal imaging can serve to support a diagnosis, but diagnosis of purine and pyrimidine disorders is reliant upon metabolite profiling. Confirming the diagnosis Diagnostic findings and genes responsible for disorders of purine and pyrimidine metabolism Adenosine deaminase deficiency is a result of mutations of ADA gene with the chromosomal location 20q13.11. The diagnostic metabolites are increased dAdo, dATP (RBC). Adenylosuccinate lyase is a result of mutations of ADSL with the chromosomal location 22q13.1. The diagnostic metabolites are increased S-Ado and SAICAr. AICAR-TF/IMP-CH or AICAR transformylase cyclohydrolase result from mutations of ATIC with the chromosomal location 2q35. The diagnostic metabolites are increased AICAr, SAICAr, and S-Ado. Adenylate kinase result from mutations of AK1 with the chromosomal location 9q34.1. There are no specific metabolites identified. Adenosine monophosphate deaminase affects both muscle and red blood cells. The chromosome location for mutated AMPD1 (muscle) and AMPD3 (AMPD3) are 1p21-p13 and 11pter-p13 respectively. Decreased ammonia is found after exercise induction. Aldehyde oxidase/ xanthine dehydrogenase deficiency result from mutation of AOX1 located on chromosome 2q33. Increased xanthine and decreased uric acid are found in the urine. Adenine phosphoribosyl-transferase result from mutations of APRT located on chromosome 16q24.3. Increased 2,8dhAde and Ade are found. CTP-phosphocoline cytidylyltransferase result from mutations of the PCYT1 gene located on chromosome 3q. Deoxyguanosine kinase deficiency is a mitochondrial depletion syndrome resulting from mutations of DGUOK located on chromosome 2p13. mtDNA depletion are found by liver biopsy when examined by EM. Increased uric acid is found. Dihydropyrimidinase deficiency results from mutations of DPYS located on chromosome 8q22. Metabolites found include increased dhU, dhT, U, and T. Dihydropyrimidine dehydrogenase deficiency results from mutations of DPYD located on 1p22. Metabolites found include increased U and T. Uromodulin/Tamm Horsfall protein disease results from mutations of UMOD located on chromosome 16p12.3. Hypoxanthine-guanine phosphoribosyl-transferase results from HPRT1 located on chromosome Xp26-q27.2. LND is completed loss of this enzyme, whereas HRND and HRG arise from partial loss. Metabolites include increased UA and hyp. IMP dehydrogenase deficiency results from mutations of IMPDH1 and IMPDH2 located on 7q31.3q32 and 3q24.2-p21.2 respectively. Metabolites include increased IMP and decreased GMP. Inosine triphosphohydrolase results from mutations of ITPA located on chromosome 20p. Metabolites include increased ITP in RBCs. Methylthioadenosine phosphorylase arises from mutations of MTAP located on chromosome 9q21. Metabolites found in cancer cells and is increased MTAdo. Aldehyde oxidase/xanthine dehydrogensase and sulfite oxidase arise from mutations of MOCS1, MOCS2 and GEPH located on chromosomes 6p21.3, 5q11 and 14p24 respectively. Metabolites found include increased xan, sulfite, thiosulfate, s-sulfocystine, and decreased cystine and UA. Purine nucleoside phosphorylase results from mutations of NP located on chromosome 14q13.1. Metabolites found include increased (d)Ino, (d)Guo, dGTP and decreased UA. Phosphoribosyl-pyrophosphate synthase results from mutations of PRPS1 and PRPS2 located on Xq22-q24 and Xp22 respectively. Metabolite found is increased UA. S-Adenosyl-homocysteine hydrolase deficiency results from mutations of AHCY located on chromosome 20cen-q13.1. Metabolite found is increased SAH. Thiopurine methyltransferase results from mutations of TPMT located on chromosome 6p22.3. Metabolites found are increased thiopurine nucleotides. Thymidine kinase 2 deficency results from mutations of TK2 located on chromosome 16q22. Main finding is found on liver biopsy i.e. mitochondrial depletion. Thymidine phosphorylase deficiency results from mutations of ECGHF1 located on chromosome 22q13.32. Main metabolites found are increased thymidine, uridine, and deoxyuridine. Depleted mitochondria are also found on liver biopsy examined by EM. Uridine monophosphate hydrolase results from mutations of UMPH1 located on 7p15-p14. Increased pyrimidine nucleotides are found in RBC. UMPS synthase deficiency results from mutations of UMPS located on chromosome 3q13. Deficiency of this enzyme lead to subtypes orotate phosphoribosyltransferase deficiency and orotidylic acid decarboxylase deficiency. Decreased uric acid is main metabolite found. Ureidopropinase deficiency results from mutations of UPB1 located on chromosome 22q11.2. Increased dhU, dhT, NC-BALA, and NC-BAIB. metabolites found. Xanthine dehydrogenase deficiency results from mutations of XDH on chromosome 2p22-p23. Metabolites found include increased xan and decreased UA. If you are able to confirm that the patient has a disorder of purine or pyrimidine metabolism, what treatment should be initiated? The treatment for a disorder of purine or pyrimidine metabolism depends on the specific enzyme deficiency or superactivity. ADA: bone marrow transplantation and enzyme replacement with PEG-ADA. There are current gene therapies for patients with ADA. Results to this point have been encouraging. ADSL no effective treatment has been identified. AICAR-TF/IMP-CH no effective treatment has been identified. Adenylate kinase treatment is supportive care of the hemolytic anemia resulting in this condition with transfusion. Adenosine monophosphate deaminase deficiency is treated with ribose and xylitol. Aldehyde oxidase and xanthine dehydrogenase deficiency are treated with allopurinol, high fluid intake, low purine diet, and avoidance of alkalis. Adenine phosphoribosyltransferase is treated with allopurinol, high fluid intake and avoidance of alkalis. CTP phosphcholine cytidylyltransferase deficiency doesn’t have an established treatment. Deoxyguanosine kinase deficiency is treated with supportive care, i.e., appropriate fluids and seizure management. Liver transplantation is an area of debate in these patients. Familial juvenile hyperuricaemic nephropathy is treated with allopurinol, high fluid intake and a low purine diet. Hypoxanthine-guanine phosphoribosyltransferase deficiency is also treated with allopurinol, high fluid intake and a low purine diet. Inosine monophosphate dehydrogenase type I deficiency (IMPDH I) has the main manifestaton of Retinitis Pigmentosa and there is no specific treatment. Molybdenum cofactor deficiency (combined AO, XDH and SO) also doesn’t have any specific treatment. Purine nucleoside phosphorylase deficiency is treated by bone marrow transplant. Phosphoribosylpyrophosphate synthase superactivity is treated with allopurinol, high fluid intake and low purine diet as well as alkalinization of the urine. S-Adenosylhomocysteine hydrolase deficiency is treated with BMT. Thiopurine methyltransferase deficiency is treated by dose adjustment of medications increasing thiopurine nucleotides in their metabolism. Xanthine dehydrogenase deficiency is treated with high fluid intake and a low purine diet. Activation induced cytidine deaminase deficiency (hyper IgM syndrome type II) is treated by controlling infections. Dihydropyrimidinase deficiency is treated by avoiding and withdrawing offending drugs. Uridine monophosphte hydrolase deficiency is treated by splenectomy. Uridine monophosphate hydrolase superactivity and synthase deficiency are treated with uridine. What are the adverse effects associated with each treatment option? The main treatment for disorders of purine and pyrimidine metabolism include avoidance of particular medications/foods/substances with elevated levels of given purine or pyrimidine, high fluid intake, allopurinol and bone marrow transplant. The main adverse effects are related to bone marrow transplantation, i.e., rejection, intolerance of transplant regimen medications and secondary malignancies. What are the possible outcomes of disorders of purine and pyrimidine metabolism? There is a wide spectrum of outcomes for patients with disorders of purine and pyrimidine metabolism. The greatest success are in patients with subtypes of these disorders which are curable by simple avoidance of drugs such as 6TPMT and in patients cured of their disease by transplant as is the case with ADA deficiency. How do these pathogens/genes/exposures cause the disease? How do genetic changes cause the disease? Mutations in a large number of genes can lead to disorders of purine and pyrimidine metabolism by causing a loss of function of necessary enzymatic activity. Other clinical manifestations that might help with diagnosis and management The diagnosis of pyrimidine and purine metabolism can be extremely difficult. Symptomatology of purine and pyrimidine metabolism can be found presenting to most medical specialties and in the absence of an obvious explanation these disorders should be considered. Patients with these disorders may have findings affecting the following systems (in addition to those previously mentioned): -Neurologic: autism, ataxia, choreoathetosis, polyneuropathy, myopathy, cramps, muscle weakness -GI: emesis, diarrhea, malabsorption, diverticulosis -Neonatology: deafness, blindness, microsomia, neonatal hepatitis -Ophthalomology: optic nerve atrophy, fundus hypopigmentation, megalocornae -Oncology: neoplasms -Orthopedics: scoliosis -Other: alopecia, apparent life threatening event (ALTE) Are additional laboratory studies available; even some that are not widely available? Patients with any suspected inborn error of metabolism should have the following studies of blood and urine: 1) Ammonia 2) Venous blood gas/lacate/UA 3) Comprehensive metabolic panel (including magnesium and phosphorus) 4) CBC 5) Uric Acid 6) Urine organic acids/urine orotic acids 7) Urine amino acids 8) Carnitine level 9) Urinary sulfites 10) Plasma amino acids 11) CSF amino acids if patient is seizing 12) Carnitine panel ► Important.If patient presents after the newborn period metabolic screen should be reviewed. If above are negative and the patient has delayed development without physical abnormalities suggestive of a genetic syndrome, a high resolution array should be sent. If patient is dysmorphic, array should be sent in the initial evaluation. How can disorders of purine and pyrimidine metabolism be prevented? Prenatal counseling and testing of known carrier parents. Avoidance of foods and medications containing offending substrates as discussed above. What is the evidence? 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Ongoing controversies regarding etiology, diagnosis, treatment The main controversy related to purine metabolism relates to gene therapy. While there has been success with gene therapy in ADA patients with SCID who have been treated with gene therapy have developed lymphoma as the result of constitutive activation of oncogenes with the insertion of the vector carrying the gene of interest. While this concern applies to gene therapy in general, it is of specific concern to this set of disorders, as the greatest success in gene therapy has come in treating ADA deficiency.

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