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Defects in metabolism of purines and pyrimidines

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Defects in the metabolism of purines and pyrimidines are not well-known in the general hospital. For this reason relatively few patients suffering from these diseases are being diagnosed. However, at present 27 different defects of purine- and pyrimidine metabolism have already been documented. Clinically, these defects are not easily recognised, at least for the larger part, because of non-specific symptoms. Therefore, the assistance of a clinical chemistry laboratory specialized in inborn errors is indispensable to discover most of these defects. This review describes the various biochemical and clinical aspects of the defects of purine and pyrimidine metabolism and provides a guide for their detection, diagnosis and treatment.

Definition and frequency

Defects of purine and pyrimidine metabolism are characterized by abnormal concentrations of purines, pyrimidines and/or their metabolites in cells or body fluids due to a decreased or an increased activity of an enzyme involved in this metabolism. Symptomatology in these defects is highly variable from very severe to relatively mild and may present at any age.
Until now about 835 patients have been diagnosed in a population of 435 x 10^6 in 18 European countries. Of these patients 70% have been detected in only 3 countries where adequate laboratory facilities are available (1). Moreover, the finding of more than 50 patients with one of the relatively newly discovered pyrimidine degradation defects in a relatively short period of 15 years suggests that at least some of these defects are not very rare (2).

Etiology and pathogenesis

Purines and pyrimidines are the building blocks of DNA and RNA, the basic elements of the cell programming machinery. In addition they fulfill a variety of functions in the metabolism of the cell of which the most important are regulation of cell metabolism and function, energy conservation and transport, formation of coenzymes and of active intermediates of phospholipid and carbohydrate metabolism. Therefore, in case a defect exists, any system can be affected.

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To date 27 defects of purine and pyrimidine metabolism have been documented. They are listed in Tables 1 and 2.

Diagnosis

In purine metabolism uric acid is the end product of biosynthesis 'de novo', salvage and degradation and therefore measurement of uric acid in plasma and urine will lead to an indication for several purine defects but certainly not all defects (table 1). Pyrimidine metabolism does not have such an end product. Moreover, as in many inborn errors of metabolism clinical symptomatology is aspecific and highly variable (Table 3). Therefore, screening methods covering a broad spectrum of purine and pyrimidine metabolites will provide the best possibility of detecting most of the known defects or even new defects. Such methods are already operative in many centres around the world for amino acids, organic acids, mucopolysaccharides and oligosaccharides. However, unfortunately only a limited number of centres screen for purines and pyrimidines, although appropriate methods are also available for this area of the metabolism. These methods are summarized in Table 4. Urine is the preferential material for screening of abnormal purine and pyrimidine metabolism as in this body fluid all waste products accumulate. In case urine is not available, plasma or CSF can be used. For tissue-specific abnormalities like the deficiencies of myo-AMDP, eryAMDP, eryITPA, cancer cell MTAP or ery-UMPH-1, and the superactivities of cancer cell IMPDH and fibroblast PU-5'N (see tables 1 and 2), the relevant tissues have to be investigated.
Confirmation of the diagnosis has to be carried out by enzyme analysis and/or mutation analysis.

Therapy

Patiens with ADA or PNP deficiency can be treated with bone marrow transplantation which provides B and T cells with sufficient enzyme activities to prevent the accumulation of the toxic nucleosides and nucleotides. This will also lead to restoration of the activity of S-adenosyl-homocysteine hydrolase (SAHH) which is secondarily inhibited by these accumulating substances. Initial treatment is done by repeated transfusions with irradiated erythrocytes. In ADA deficient patients enzyme replacement therapy is also possible with PEG-ADA (bovine ADA coupled to polyethylene glycol) injected intramuscularly. Gene therapy has been tried in ADA deficient patients with only limited success, but it is expected that adequate gene therapy will become available for both diseases in the near future (16).
Patients with a deficiency of XDH (xanthinuria type I),

Table 1. Defects of purine metabolism with their synonyms, abbreviations and diagnostically important metabolites

Defect	Synonym	Abbreviation	Index metabolites
Adenosine deaminase deficiency	SCID	ADA	(d)Ado↑, (d)ATP↑(RBC)
Adenosine deaminase superactivity	ADA-superactivity	ADAs	none
Adenylate deaminase deficiency: muscle : AMPD-1 erythrocyte: AMPD-3	AMP-deaminase def. myoAMPD def. eryAMPD def.	AMPD AMPD-1 AMPD-3	NH3↓ (exercise test)
Adenylo succinate lyase deficiency	adenylosuccinase	ASL	s-Ado↑, s-AICAR↑
Aldehyde oxidase + XDH deficiency	xanthinuria-II	AO/XDH	(hypo-)xanthine↑, uric acid↓
Adenine phosphorib. transferase def.	2,8-diOH-adeninuria	APRT	2,8-diOH-adenine↑
Familial juvenile hyperuricemic nephropathy	juvenile gout	FJHN	uric acid↑
Hypoxanthine-guanine phosphoribosyl transferase deficiency: complete deficiency partial deficiency	 Lesch-Nijhan synd. Kelley-Seegmiller	 HGPRT HGPRTp	 uric acid↑, hypoxanthine↑ uric acid↑
Inosine monophosphate dehydrogenase type-II superactivity	cancer cell IMPDH	IMPDHs-II	IMP↑/GMP↓ (cancer cells)
Inosine triphosphate pyrophosphohydrolase deficiency	ery-ITPA deficiency	ITPA	ITP↑(RBC)
Methylthioadenosine phosphorylase deficiency	cancer cell MTAP deficiency	MTAP	MTAdo↑(in cancer cells)
Molybdenum cofactor deficiency (combined deficiency of AO, XDH and SO)	xanthinuria-III (xanthinuria-sulfituria)	MCF (AO/XDH/SO)	(hypo-)xanthine↑, sulfite↑ thiosulfate↑, s-sulfocys↑ cystine↓, uric acid↓
Phosphoribosylpyrophosphate synthase superactivity	PRPS superactivity	PRPSs	uric acid↑
Purine nucleoside phosphorylase deficiency	PNP deficiency	PNP	(d)Ino↑, (d)Guo↑ dGTP↑(RBC), uric acid↓
Purine-5[1]Nucleotidase superactivity	fibroblast Pu-5N	Pu-5[1]Ns	-
S-Adenosylhomocysteine hydrolase deficiency	occurs in: ADA, PNP and HGPRT deficiency	SAHH	S-adenosylhomocys↑(RBC)
Thiopurine methyltransferase deficiency	TPMT deficiency	TPMT	thiopurine nucleotides↑(RBC)
Xanthine dehydrogenase deficiency (isolated)	xanthinuria-I	XDH	(hypo-)xanthine↑ uric acid↓

Index metabolites increased (↑) or decreased (↓) in body fluids or in indicated cell type. (d)Ado, (d)Guo, (d) Ino, (d)ATP: (deoxy-) adenosine, -guanosine, -inosine, -adenosine triphosphate; s-Ado, s-AICAR: succinyladenosine, aminoimidazole carboxamide riboside; SAH: S-adenosylhomocysteine.

APRT, FJHN, HGPRT or HGPRTp (KS), or patients with a superactivity of PRPS should be treated with a.o. allopurinol in order to decrease the production of the poorly-soluble substances (xanthine, 2,8-dihydroxyadenine or uric acid) accumulating in these diseases. Additional measures like high fluid intake, alkalinisation of the urine by administration of bicarbonate or citrate (not successful in APRT deficiency) and a low-purine diet may be necessary in order to prevent cristallization. Patients with AMDA-1 deficiency should be advised to avoid heavy exercise in order to prevent rhabdomyolytic attacks and myoglobinuria. In some patients treatment with ribose seems to improve exercise tolerance (17).

Patients with TPMT, PU-5'N (18), MCF, XDH-AO, UMPS, DPD or DHP deficiency or their relatives should be informed about the pharmacogenetic consequences of their defect. They should avoid drugs being a substrate or precursor of the substrate for the defective enzyme or receive a dosis adapted to the residual activity of that enzyme. Patients with UMPS deficiency can be treated with uridine which is

Table 2. Defects of pyrimidine metabolism with their synonyms, abbreviations and diagnostically important metabolites

Defect	Synonym	Abbreviation	Index metabolites
β-Alanine-α-ketoglutarate aminotransferase deficiency	GABA-AT def[1)], β-alaninuria	BAKAT	β-alanine↑
β-Aminoisobutyrate-pyruvate aminotransferase deficiency	hyper-β-amino-isobutyric aciduria	BAIBPAT	β-aminoisobutyrate↑
Cytidine diphosphate-choline phosphotransferase deficiency	ery CDP-CPT-deficiency	CDP-CPT	CDP-choline + CDP ethanolamine↑(RBC)
Dihydropyrimidinase deficiency	dihydropyrimidinuria	DHP	DHU↑, DHT↑, Uracil s↑ thymine s↑
Dihydropyrimidine dehydrogenase deficiency	thymine-uraciluria	DPD	uracil↑, thymine↑,
Pyrimidine 5[1] nucleotidase deficieny	UMPH-1 deficiency	Py-5[1]N	pyr. nucleotiden↑(RBC)
Ureidopropionase deficiency	NC-BALA amido-hydrolase deficiency	UP	NC-BALA↑, NC-BAIB↑
Uridine monophosphate hydrolase deficiency	see Py-5[1]N	UMPH-1	pyr. nucleotiden↑(RBC)
Uridine monophosphate synthase deficiency:	orotic aciduria	OPRT-ODC (UMPS)	
Orotate phosphoribosyl-transferase deficiency	OA type I	OPRT	orotic acid↑
Orotidylic acid decarboxylase deficiency	OA type II	ODC	orotic acid↑, orotidine↑

Index metabolites increased (↑) , slightly increased (s↑) or decreased (↓)in body fluids or in indicated cell type. NC-BALA and NC-BAIB: N-carbamyl-β-alanine and N-carbamyl-β-amino-isobutyric acid; DHU: dihydrouracil; DHT: dihydrothymine; OA: orotic aciduria

converted to UMP by uridine kinase. Uridine supplementation results in hematologic remission and acceleration of growth but does not prevent suboptimal physical and mental development (19).
Therapy for the other defects mentioned in Table 1 has not yet been established.

Inheritance and prevention

In most of the defects of purine and pyrimidine metabolism inheritance is autosomal recessive. Exceptions are PRPS superactivity and HGPRT deficiency which are X-linked, ADA deficiency being X-linked in 1/3 and autosomal recessive in 2/3 of the patients, and FJHN in which inheritance is autosomal dominant. Mutation analysis has been reported in nearly all defects, but the great number of different mutations and the occurrence of many new mutations does not allow carrier detection with 100% certainty. For these reasons also antenatal diagnosis by mutation analysis is difficult, unless mutant alleles can be detected by automated direct DNA sequencing of genomic DNA. Prenatal diagnosis by metabolite or enzyme analysis is available for most of the defects using chorionic villi, amniotic fluid or amniotic fluid cells, or fetal blood (20).

Table 3. Main symptomatology associated with the 27 defects of purine and pyrimidine metabolism. Defects concern enzyme deficiencies except ADAs, PRPSs, PU-5[1]Ns and IMPDHs-II which present with superactivity. (For abbreviations see tables 1 and 2)

Renal problems/cristaluria	PRPSs, HGPRT, HGPRTp, APRT, PNP, XDH, XDH-AO, MCF, FJHN, UMPS
Psychom. retardation	PRPSs, ASL, HGPRT, Pu-5[1]Ns, PNP, MCF, UMPS, DPD, DHP, UP
Epileptic/convulsive disease	ASL, Pu-5[1]Ns, MCF , DPD, DHP, UP, BAKAT
Pharmacogenetic syndrome	TPMT, PU-5[1]N, MCF, XDH-AO, UMPS, DPD, DHP
Immunological problems	ADA, PNP, (SAHH), Pu-5[1]Ns, UMPS
Anemia	ADAs, UMPS, Py-5[1]N, CDP-CPT
Growth retardation	ADA, ASL, DPD, UMPS
Autistic features	PRPSs, ASL, DPD
Cancer	IMPDHs-II, MTAP
None: benign polym.	ITPA, BAIBPAT
Arthritis	PRPPs, HGPRTp
Lymphopenia	ADA, PNP
Exercise intolerance, rhabdomyolysis	AMPDA
Ataxia, selfmutilation	HGPRT
Inherited sensorineural deafness	PRPSs

Table 4. Screening methods for the detection of defects of purine and pyrimidine metabolism

Screening method	Detectable defects	References
Analysis of uric acid in plasma and urine	see table 1	3
2-Dim-TLC after isolation and prefractionation of urine	all defects with altered metabolite concentration	3, 4
HPLC of urine and (diode array) UV detection	id.	3
Cation-exchange chromatography for amino-acids with on-line UV detection	XDH, XDH + AO and XDH + AO + SO (MCF)	5
Amino-acids analyses before and after acid hydrolysis of urine	ASL, DHP, UP, BAKAT and BAIBPAT	6,7
GC-MS of trimethylsilylated organic acid extracts of urine	DPD, DHP, UMPS	7, 8, 9
HPLC-(FAB/ESI)-MS of urine	DPD, DHP	9, 10
H-NMR spectroscopy of urine	ASL, DHP, DPD, HGPRT, PNP and XDH	11
UV-spectral analysis of deproteinized erythrocyte extracts	CDP-CPT and Py-5'N (UMPH-1)	12, 13
HPLC of nucleotides in erythrocytes	ADA, HGPRT, IMPDHs-II, ITPA, PNP, Py-5'N	12, 13, 14
Semi-ischemic muscle exercise test with determination of NH3 and lactate in blood	AMPDA-1	15

Conclusions and recommendations

As in many inborn errors of metabolism, the causal relationship between clinical symptoms and biochemical abnormalities in purine and pyrimidine disorders is not yet clear. Moreover, in most defects the symptomatology is highly aspecific and onset can occur at any age. Therefore, screening for defects of purine and pyrimidine metabolism is indicated in patients with one of the symptoms mentioned. The finding of more than 50 patients with pyrimidine degradation defects in a relatively short period suggests that these defects are not rare. Some defects can even in the heterozygous state lead to severe toxic reactions during treatment with purine or pyrimidine analogues (e.g. azathioprine in TPMT deficiency and 5-fluorouracil in partial and complete DPD deficiency). For some enzymes, defects have not yet been detected. Some of these defects can be expected to be lethal when complete, but in that case partial defects still have to be found. However, the successful recognition of the well-known defects and of new defects of purine and pyrimidine metabolism strongly depends on the availability of screening methods in diagnostic laboratories. It requires adequate knowledge of the field and close collaboration between clincians and biochemists

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