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REVIEW

Uric acid changes in urine and plasma: An effective tool in screening for purine inborn errors of metabolism and other pathological conditions

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Summary Purine inborn errors of metabolism (IEM) are serious hereditary disorders, which should be suspected in any case of neonatal fitting, failure to thrive, recurrent infections, neurological deficit, renal disease, self-mutilation and other manifestations. Investigation usually starts with uric acid (UA) determination in urine and plasma. UA, the final product of purine metabolism in humans, may be altered not only in purine IEM, but also in other related pathologies and clinical conditions. However, data and information about abnormal UA levels are scattered in the literature, often being controversial and confusing. A comprehensive overview has been elaborated, according to abnormal UA levels in urine and plasma, which associates these alterations with purine IEM. Other possible diseases, clinical conditions, diet and drug intake, related to the metabolism of uric acid, are also presented. The article includes tables that classify the disorders according to different patterns of UA alterations, with pertinent enzymes, clinical symptoms, inheritance and comments. Additionally, summarized pathophysiological mechanisms of important disorders are described. The overview is intended to assist in the interpretation of the results of UA analyses. It demonstrates that variation of UA concentrations in urine and plasma may constitute an effective tool in screening for purine IEM and other related pathological conditions.

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References to electronic databases: OMIM 300322; OMIM 229600; OMIM 603027; OMIM 232400; OMIM 232600; OMIM 232800; OMIM 201450; OMIM 220150; OMIM 232200; OMIM 162000; OMIM 164050; OMIM 278300.

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Abbreviations

ADA	adenosine deaminase
ADSL	adenylosuccinate lyase
APRT	adenine phosphoribosyltransferase
FJHN	familial juvenile hereditary nephropathy
GSD	glycogen storage disease
Gua	guanine
HDL	high-density lipoprotein
HPRT	hypoxanthine–guanine phosphoribosyltransferase
Hx	hypoxanthine
IEM	inborn errors of metabolism
IMP	inosine monophosphate

LND	Lesch–Nyhan disease
MAD	myoadenylate deaminase
MCAD	medium-chain acyl-CoA dehydrogenase
PNP	nucleoside phosphorylase
PP-R-P	5-phosphoribosyl-1-pyrophosphate
PRS	5-phosphoribosyl-1-pyrophosphate synthetase
UA	uric acid
Xa	xanthine
XDH	xanthine dehydrogenase
XO	xanthine oxidase

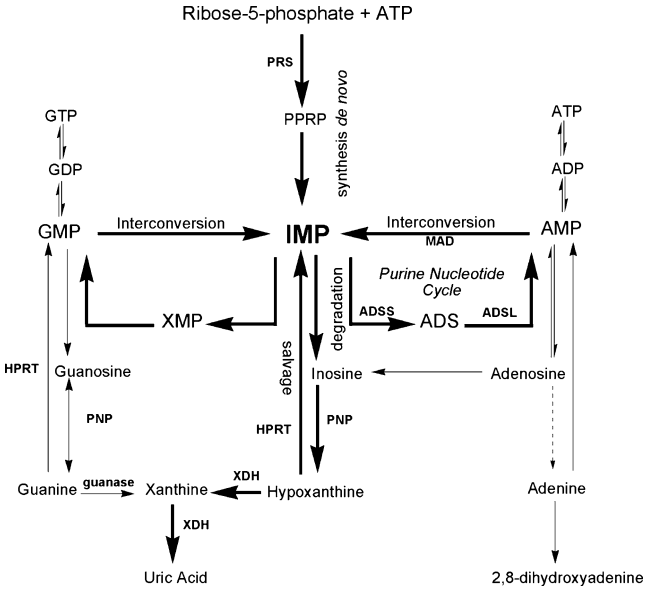

Fig. 1 Human purine metabolism. Pertinent pathways: formation of the purine nucleotide inosine monophosphate (IMP) from non-purine precursors (synthesis *de novo*), or purine bases (salvage reactions); purine nucleotide interconversion reactions; degradation to the end product uric acid (catabolic reactions). PP-R-P=5-phosphoribosyl-1-pyrophosphate; PRS=5-phosphoribosyl-1-pyrophosphate synthetase; PNP=purine nucleoside phosphorylase; XDH=xanthine dehydrogenase; HPRT=hypoxanthine-guanine-phosphoribosyltransferase; AMP, ADP and ATP=adenosine mono-, di-, and triphosphates; GMP, GDP and GTP=guanosine mono-, di-, and triphosphates; XMP=xanthosine monophosphate; ADS=adenylosuccinate; ADSS=adenylsuccinate synthetase; ADSL=adenylosuccinate lyase; MAD=myoadenylate deaminase

Introduction

Uric acid (UA) is the final product of purine metabolism in humans. Purine bases are constituents of nucleotides, which undergo a continuous process of synthesis, interconversion and breakdown. The catabolic reactions lead to the free purine bases adenine, guanine, hypoxanthine and xanthine, which is oxidized to UA. Deficient, absent or exacerbated activities of the numerous enzymes involved result in various inherited metabolic disorders. These are known as purine inborn errors of metabolism (IEM), and are characterized by abnormal concentrations of UA, purines and/or other metabolites in cells and body fluids. Pertinent pathways of human purine metabolism are shown in Fig. 1.

Purine IEM comprise a broad group of disorders with high clinical impact, great variability of presentation and considerable genetic heterogeneity. They should be suspected in any case of neonatal fitting, failure to thrive, mental and growth retardation, recurrent infections, self-mutilation, neurological deficit, renal disease and/or kidney stones, muscle weakness and others manifestations. Family history, consanguinity and adverse reactions to drugs that are purine analogues also need to be considered. Identification is difficult, since these disorders may affect any system—neurological, immunological, haematological, renal and others (Simmonds et al 1997). Moreover, since numerous clinicians are not familiar with defects in the metabolism of purines, many patients suffering from these diseases may be misdiagnosed or remain undiagnosed (Simmonds et al 1997; Van Gennip 1999).

Uric acid is one of the diagnostically most important metabolites. Investigation of purine IEM usually starts by quantitative determination of UA in urine, as the UA/creatinine ratio (Duran 2002; Duran et al 1997). However, correct diagnosis requires evaluation of UA in both urine and plasma (Duran et al 1997; Simmonds et al 1997). In addition, local control ranges for healthy individuals (adults and children) must be established, taking into account that neonates and infants under 2 years of age may present with UA overexcretion. Special attention must be paid to diet and drug intake, sample handling and storage and bacterial contamination in the collecting bottle (Simmonds et al 1997). Measurement of UA concentration is important not only for the detection of purine IEM. Altered UA levels in urine and plasma may indicate other related disorders and pathological conditions, and may also result from diet and drug intake.

Following the UA analyses, results must be evaluated and interpreted. However, data and information about abnormal UA levels in urine (U) and sometimes in plasma (P) are scattered in the literature, often being controversial and confusing. In the present work, we elaborated a comprehensive overview, according to abnormal UA levels in *urine* and in *plasma,* which associates these alterations with purine IEM and other pathological conditions. Tables are presented classifying

the disorders according to different patterns of UA alterations, with pertinent enzymes, clinical symptoms, inheritance and comments. Summarized pathophysiological mechanisms of important disorders are also described. Data were obtained by bibliographic review of the last 15 years, by direct search, by cross-referencing and by the Medline system.

The overview is intended to assist in the interpretation of the obtained UA levels in urine and plasma, providing important data to facilitate diagnosis. Owing to the varied sources of information, both the terms *urate* and *uric acid* are used. In fact, at physiological pH, 98–99% of the molecules are in the form of urate; uric acid exists only in parts of the urinary tract, where pH is less than 5.7 (Emmerson 1996). Data on urinary alterations are sometimes conflicting. Renal excretion of UA is an extremely complicated physiological function, consisting of filtration, secretion and reabsorption steps; only 8–12% of the original load appears in the final urine (Becker 2001; Sperling 2001). Interference may occur in any of these steps, resulting in altered excretion. It must be noted that, at present, the regular model for renal UA handling is being re-evaluated (Terkeltaub et al 2006).

Different categories of abnormal UA levels in urine and plasma are presented in the following. They include pertinent purine IEM, other disorders and summarized pathophysiological mechanisms.

Hyperuricosuria (UA) U↑ and hyperuricaemia (UA) P↑

This category comprises two groups. In the first—purine inborn errors of metabolism—UA overproduction occurs owing to altered activity of an enzyme: (1) overactivity or deficiency, in the pathways of synthesis *de novo* or salvage reactions (Fig. 1); (2) deficiency, in the pathway of IMP (inosine monophosphate) formation from AMP (adenosine monophosphate) in the purine nucleotide cycle (Fig. 1).

UA is synthesized mainly in the liver and circulates relatively free of protein binding, so that nearly all the urate produced is available for filtration at the glomerulus. The increased urinary UA excretion is consistent with increase in plasma levels (Becker 2001; Terkeltaub et al 2006).

This group includes *Lesch–Nyhan disease (LND)* and *Kelley–Seegmiller syndrome*, characterized by severe and partial deficiency of HPRT (hypoxanthine–guanine phosphoribosyltransferase), respectively; *PRS superactivity*, caused by overactivity of PRS (5-phosphoribosyl-1-pyrophosphate synthetase). In these disorders UA overproduction is a consequence of increased availability of PP-R-P (5-phosphoribosyl-1-pyrophosphate), in the pathway of purine synthesis *de novo* (Becker 2001). *MAD deficiency* results from deficiency of MAD (myoadenylate deaminase) in the pathway of IMP formation from AMP in the purine nucleotide cycle (Fig. 1). Disruption of the cycle leads ultimately to net ATP degradation with consequent UA overproduction (Sabina and Holmes 2001; Tarnopolsky et al 2001).

In *Lesch–Nyhan disease* (OMIM 300322), complete deficiency of the purine salvage enzyme HPRT results in accumulation of its substrates guanine (Gua) and hypoxanthine (Hx), which are degraded and excreted ultimately as UA (Fig. 1). UA overproduction results from the combination of increased purine synthesis with failure of purine recycling (Jinnah and Friedmann 2001). Despite this overproduction, marked UA increase in serum levels is prevented by efficient renal clearance. Therefore, urinary measurements provide a more accurate estimate of total UA production. Patients with LND usually exhibit elevated UA/creatinine ratio.

Data pertinent to the pattern 'hyperuricosuria (UA) U↑ and hyperuricaemia (UA) P↑', related to the first group, can be found in Table 1a.

The second group comprises hereditary disorders, which originate in non-purine metabolic pathways, also resulting in elevated UA levels in urine and plasma. Some pertinent disorders are described below.

Primary hyperuricaemia, gout and asymptomatic hyperuricaemia are conditions in which the mechanisms leading to UA overproduction are heterogeneous and biochemical defects remain to be elucidated (Becker 2001). In the majority of gout patients, hyperuricaemia is derived from undefined variations in genetically determined metabolic and renal functions (Scott 1996). *Asymptomatic hyperuricaemia* is the condition in which, despite abnormally high urate concentration, symptoms have not occurred. Manifestations may arise, but only after 20 or 30 years of sustained hyperuricaemia and in a minority of hyperuricaemic individuals. Increased urinary UA excretion is demonstrable in 10–15% of patients with gout and primary hyperuricaemia (Becker 2001).

In the remaining disorders, UA overproduction is due to nucleotide depletion. Net ATP degradation may result from either increased ATP consumption or impaired ATP regeneration. When the supply of inorganic phosphate (Pi), oxygen, glucose or fatty acids is limited, ATP synthesis may be impaired,

Table 1a Hyperuricosuria (UA)↑ and hyperuricaemia (UA)↑—Purine inborn errors of metabolism with uric acid (UA) overproduction

UA (U)	UA (P)	Disorders	Enzymes	Comments	Manifestations	Inheritance	References
↑	↑	Lesch–Nyhan syndrome	HGPRT complete deficiency	UA overproduction and overexcretion Children may have normal (UA/P) due to high UA clearance	Choreoathetosis, spasticity, mental/growth retardation, haematuria, urolithiasis, acute renal failure, self-mutilation	X-linked	a, b, c, d, e
↑	↑	Kelley–Seegmiller syndrome	HGPRT partial deficiency	UA overproduction and overexcretion	Early adult onset in men: gouty arthritis, some Lesch–Nyhan symptoms. Mild or no neurological symptoms	X-linked	a, b, c, d, e
↑	↑	PRS overactivity	PRS	UA overproduction, due to increased PRPP availability UA overexcretion	Early onset: severe neurodevelopmental impairment, deafness Late juvenile: males—gout or urolithiasis, no neurological deficit	X-linked	a, b, c, e, f
↑ or N	↑	MAD deficiency	Myoadenylate deaminase	Impairment of ATP generation in muscle Exercise: increased ATP degradation → UA; failure to produce NH_3 and IMP	Inherited: asymptomatic or exercise-related muscle cramps and myalgia. Acquired: other neuromuscular or rheumatological disorders	Autosomal recessive or acquired	c, g, h, i, j

↑=increased; HGPRT=hypoxanthine–guanine phosphoribosyltransferase; PRS=5-phosphoribosyl-1-pyrophosphate synthetase; PP-R-P=5-phosphoribosyl-1-pyrophosphate.
References: (a) Simmonds et al (1997), (b) Van Gennip (1999), (c) Becker (2001), (d) Jinnah and Friedmann (2001), (e) Simmonds and Van Gennip (2002), (f) Duran (2002), (g) Chen (2001), (h) Sabina and Holmes (2001), (i) Pantoja-Martinez et al (2004), (j) Tarnopolsky (2002).

provoking severe ATP depletion and consequent hyperuricaemia (Becker 2001).

Conditions that result in disordered ATP metabolism include *hereditary fructose intolerance* (OMIM 229600), in which fructose triggers rapid breakdown of purine nucleotides to UA, in liver, causing hyperuricaemia and hyperuricosuria (Ali et al 1998; Steinmann et al 2001); *fructose-1,6-biphosphatase deficiency* (OMIM 603027), a disorder of gluconeogenesis, mainly in liver (Steinmann et al 2001); *glycogen storage disease (GSD)types III, V and VII* (OMIM 232400, 232600, 232800), characterized by abnormal muscle glycogen metabolism (Becker 2001; Tarnopolsky 2002); and *MCAD (medium-chain acyl-CoA dehydrogenase) deficiency*.

In *MCAD deficiency* (OMIM 201450), hypoglycaemia resulting from reduced glucose intake or depletion provokes entry of free fatty acids into mitochondria. The defective MCAD enzyme impairs oxidation of medium-chain fatty acids and production of ketones. Accumulated fatty acid intermediates inhibit gluconeogenesis: ATP production is impaired, and nucleotide depletion results in UA overproduction (Medium Chain Acyl-CoA Dehydrogenase Deficiency 2006; Tarnopolsky 2002).

Data pertinent to the pattern 'hyperuricosuria (UA) U↑ and hyperuricaemia (UA) P↑' related to the second group can be found in Table 1b.

In addition to the inherited disorders presented in Tables 1a and 1b, alterations of uric acid levels in urine and plasma may also be seen in a number of other diseases and clinical conditions, and in situations resulting from altered renal excretion, diet and drug intake. The possible diseases and situations are listed below, with comments.

UA overproduction

Enhanced nucleic acid turnover

Paget's bone disease (osteitis deformans): UA levels are increased in about 30% of patients (Carbone and Barrow 2006; Chow and Slipman 2006; Schneider et al 2002).

Hyperphosphatasia (juvenile Paget disease or Bakwin–Eiger syndrome): Greatly increased bone resorption/formation (Cundy et al 2002; Paget Disease Juvenile Type 2005).

Table 1b Hyperuricosuria (UA)↑ and hyperuricaemia (UA)↑—hereditary disorders in non-purine metabolic pathways, with uric acid (UA) overproduction

UA (U)	UA (P)	Disorders	Enzymes	Comments	Manifestations	Inheritance	References
↑ or N	↑	Asymptomatic hyperuricemia	—	Risk for gout related to age, sex, duration and degree of hyperuricaemia	Most persons remain asymptomatic, even after years of hyperuricaemia	Multiple genetic determinants	a, b
↑ 10 or 15% of patients	↑ or N	Primary hyperuricemia–idiopathic gout	—	Biochemically and genetically heterogeneous UA overproduction: increased purine synthesis UA overexcretion	Symptoms in a minority of uricaemic persons and only after 20–30 years of sustained hyperuricaemia Acute arthritis, tophus, urate/UA nephropathies, crystal deposits, UA urolithiasis	Multiple genetic determinants	a, c, d
↑	↑	Hereditary fructose intolerance	Fructaldolase B	Gluconeogenesis and glycogenolysis impaired. ATP depletion: increased ATP degradation → UA	Fructose intake: vomiting, severe hypoglycaemia Prolonged intake: liver/renal failure, vomiting, jaundice, failure to thrive, lactic acidosis	Autosomal recessive	a, d, e, f, g, h
↑	↑	Hereditary fructose-1,6-bisphosphatase deficiency	FBPase	Gluconeogenesis impaired ATP depletion: increased ATP degradation → UA	Neonates: apnoea, hyperventilation, somnolence, coma, hypoglycaemia, ketosis, lactic acidosis Later: seizures, vomiting, lethargy	Autosomal recessive	a, e, f
↑	↑	Glycogenosis III (GSD III; Cori disease)	Glycogen debranching enzyme	Impaired glucose availability for ATP generation in muscle During exercise: increased ATP degradation → UA	Hepatomegaly, myopathies, hypoglycaemia, growth retardation, hyperlipidaemia, muscular weakness Exercise: hyperammonaemia	Autosomal recessive	a, e, i, j, k
↑	↑	Glycogenosis V (GSD V; McArdle disease)	Myophosphorylase	Impaired glucose availability for ATP generation in muscle During exercise: increased ATP degradation → UA	Exercise: fatigue, intolerance, pain, cramps, muscular weakness, myoglobinuria, hyperammonaemia	Autosomal recessive	a, e, i, j, k
↑	↑	Glycogenosis VII (GSD VII; Tarui disease)	Muscle phosphofructokinase	Impaired glucose availability for ATP generation in muscle During exercise: increased ATP degradation → UA	Exercise: fatigue, intolerance, pain, muscular weakness, cramps, haemolytic anaemia; severe hyperuricaemia	Autosomal recessive	a, e, i, j, k
↑	↑	MCAD deficiency	MCAD	The most common inherited disorder of fatty acid metabolism Impaired medium-chain fatty acid oxidation; inhibition of gluconeogenesis and impaired ATP production	Fasting triggers hypoketotic hypoglycaemia; vomiting, coma, lethargy, liver disease, seizures, hypotonia, apnoea/respiratory arrest, mental retardation	Autosomal recessive	e, k, l, m, n

↑=increased; N=normal; fructaldolase B=fructose-1,6-biphosphate aldolase B (aldolase B); FBPase=fructose-1,6-bisphosphatase; GSD=glycogen storage disease; MAD=myoadenylate deaminase; MCAD=medium-chain acyl-CoA dehydrogenase; IMP=inosine monophosphate.

References: (a) Becker (2001), (b) Emmerson (2005), (c) Pittman and Bross (1999), (d) Qazi and Lohr (2005), (e) Duran (2002), (f) Steinmann et al (2001), (g) Moses (2007), (h) Perlmutter et al (2002), (i) Chen (2001), (j) Yamasaki et al (1996), (k) Tarnopolsky (2002); (l) Roe and Ding (2001), (m) Mayatepek et al (1997), (n) Medium Chain Acyl-CoA Dehydrogenase Deficiency (2006).

Psoriasis: New skin cells move from lower layers to the surface very rapidly: itchy silvery scales (Bruce 2000; Golov et al 1994).

Hemolytic anaemia: Accelerated turnover of bone marrow cells, nucleic acids and nucleotides; red blood cells are prematurely destroyed (Becker 2001; Dhaliwal et al 2004; Qazi and Lohr 2005; Weatherall et al 2001).

Myelo- and lymphoproliferative diseases; other malignancies: Rapid cell proliferation and turnover (polycythaemia vera, lymphoma, leukaemia) (Emmerson 1996; Moses 2007; Pittman and Bross 1999; Weatherall et al 2001).

Disordered ATP metabolism (impaired ATP synthesis; severe ATP depletion)

Tissue hypoxia; metabolic myopathies; acutely ill patients: Increasing plasma concentrations of purine degradation products; UA overproduction (Becker 2001; Chen HJ et al 2000; Emmerson 1996).

Rhabdomyolysis: Disintegrating muscle cells release their constituents (UA, hypoxanthine, xanthine, lactate, myoglobin) into the circulation (Criddle 2003; Pittman and Bross 1999; Vanholder et al 2000).

Hypophosphataemia: Results mostly from renal loss of phosphate; tissue hypoxia and disruption of cellular function (Subramanian and Khardori 2000).

Perinatal asphyxia: A common occurrence in the perinatal period. Lactate production induced by hypoxia; ATP degradation to UA (Chen HJ et al 2000).

Others

Hyperuricosuric autism—(UA)P not reported: Literature: UA/ Creatinine ratio elevated in 20–25% of patients (Muhle et al 2004; Page and Coleman 2000).

Hyperuricosuric autism—(UA)P not determined. A special group of idiopathic autistic children analysed in our laboratory (LABEIM). UA/creatinine ratio elevated in 51% (unpublished results).

Drugs, diet

Cytotoxic agents: Rapid liberation of nucleic acids and nucleotides; subsequent degradation to UA (e.g. cyclophosphamide) (Moses 2007; Qazi and Lohr 2005).

Fructose infusion: Within minutes, UA levels increase in plasma and later in urine. Increased ATP degradation (Becker 2001; Steinmann et al 2001).

Vitamin B_{12}: Treatment of pernicious anaemia; may lead to hyperuricosuria (Becker 2001; Moses 2007).

Pancreatic extract (high-dose therapy for cystic fibrosis): rich in purines, results in hyperuricosuria, with or without hyperuricaemia (Fathallah-Shaykh and Neiberger 2006b; Moses 2007).

Excessive dietary purine ingestion: Organ meat, seafood, beer and others result in hyperuricosuria; can be a cause of sustained hyperuricaemia. Plasma UA is usually high normal (Emmerson 1996; Fathallah-Shaykh and Neiberger 2006b; Qazi and Lohr 2005).

Hyperuricosuria (UA) U↑ and hypouricaemia (UA) P↓

This category comprises hereditary disorders in renal handling of urate, manifested in increased urate clearance. Different types of renal hypouricaemia are distinguished, according to the nature and site of the transport defect. The four-component model of renal urate handling in humans includes free glomerular filtration, early proximal tubular reabsorption, tubular secretion and postsecretory tubular reabsorption. Currently, the model is being re-evaluated (Sperling 2001; Terkeltaub et al 2006).

Hereditary (isolated) renal hypouricaemia (OMIM 220150) is an inborn error of membrane transport. Hypouricaemia and increased renal urate clearance are presumably due to defective urate reabsorption in the proximal tubule. The recently identified urate transporter URAT1 appears to be a major determinant of urate reabsorption. URAT1 has highly specific urate transport activity and is suggested to be the most potent regulator of serum urate levels. (Bordier et al 2004; Cheong et al 2005; Terkeltaub et al 2006).

The disorder must be differentiated from other hereditary conditions of renal hypouricaemia, such as Fanconi and Hartnup syndromes. In these, the urate

transport defect is only one component of a generalized membrane transport disturbance.

Data pertinent to the pattern 'hyperuricosuria (UA) U↑ and hypouricaemia (UA) P↓' can be found in Table 2. In addition, altered UA levels may be found in other disorders and conditions as listed below.

UA overexcretion

Acquired renal hypouricaemia–hyperuricosuria: Decreased tubular reabsorption or presence of endogenous or drug-derived uricosuric agents (Bordier et al 2004; Sperling 2001).

Diabetes mellitus, insulin-dependent (with poor glycaemic control): Possible interference of tubular glucose reabsorption with tubular capacity for uric acid reabsorption (Gonzalez-Sicilia et al 1997; Trave et al 1996).

Liver cirrhosis: Several reports state that hypouricaemia is due mainly to excessive uric acid renal clearance. It may also result from severe hepatocellular injury with loss of hepatic xanthine oxidase activity. Other authors: mean serum uric acid levels are increased, related closely to renal plasma flow (Lee et al 1999; Liberopoulos et al 2002).

Association with hyponatraemia

Intracranial disease (in general): Hyperuricosuria and hypouricaemia may be common features (Maesaka et al 1999; Milionis et al 2002).

SIADH (syndrome of inappropriate antidiuretic hormone) and CSWS (cerebral salt-wasting syndrome): Increased UA fractional excretion. (Berkenbosch et al 2002; Maesaka et al 1999; Milionis et al 2002; Springate 2006).

Alzheimer: Hypouricaemia and increased UA excretion have been noted in Alzheimer patients, even in absence of hyponatraemia (Maesaka et al 1993; Milionis et al 2002).

Table 2 Hyperuricosuria (UA)↑ and hypouricaemia (UA)↓—hereditary disorders in renal handling of urate, manifested in increased urate clearance

UA (U)	UA (P)	Disorders	Enzymes	Comments	Manifestations	Inheritance	References
↑	↓	Hereditary (isolated) renal hypouricaemia	—	A rare inborn error of membrane transport characterized by abnormally high renal urate clearance, presumably due to defective proximal tubular urate reabsorption Major cause of the disorder: defect in the gene which encodes the renal urate transporter protein URAT1. Most patients are clinically silent	A few patients: urolithiasis, UA nephropathy, acute renal failure (ARF), haematuria, following exercise	Autosomal recessive	a, b, c, d
↑	↓	Other hereditary renal hypouricaemias	—	The urate transport defect is only one of the components of generalized renal transport defects, such as Hartnup syndrome or diseases associated with Fanconi syndrome (Wilson, galactosaemia, cystinosis, others) Decreased urate tubular reabsorption	Variable symptoms	—	a, b, d

↑=increased; ↓=decreased.
References: (a) Simmonds et al (1997), (b) Sperling (2001), (c) Cheong et al (2005), (d) Bordier et al (2004).

AIDS: Hypouricaemia and hyponatraemia may coexist in patients. Central nervous system infections are associated with significant decreases in serum UA levels (Collazos et al 2000; Maesaka et al 1999; Milionis et al 2002).

Drugs

Uricosuric substances: Weak organic acids that increase UA renal clearance, by inhibiting renal tubular reabsorption (e.g. probenecid and salicylates (high doses), sulfinpyrazone, ascorbic acid, oestrogen) (Becker 2001; Emmerson 1996).

Bacterial contamination in the collecting bottle may result in degradation of metabolites to UA, leading to elevated urinary UA levels (Simmonds et al 1997).

Hypouricosuria (UA) U↓ and hyperuricaemia (UA) P↑

This category comprises hereditary disorders with hyperuricaemia associated secondarily with decreased uric acid (UA) excretion. Included are *primary hyperuricaemia and gout, glycogen storage disease (GSD) type Ia (von Gierke disease) and familial juvenile hereditary nephropathy (FJHN)*.

Primary hyperuricaemia and gout are, as previously described, biochemically and genetically heterogeneous, owing to multiple genetic determinants. In 80% or more of individuals with gout, impaired UA excretion is the major mechanism leading to hyperuricaemia (Becker 2001). Recent data support an important role of the urate transporter URAT1 in hyperuricaemia and gout (Terkeltaub et al 2006).

In *GSD type Ia* (*von Gierke disease*) (OMIM 232200) the hallmarks are hypoglycaemia, lactic acidosis, hyperlipidaemia and hyperuricaemia. Deficient glucose-6-phosphatase activity in liver, kidney and intestinal mucosa blocks the final steps of both gluconeogenesis and glycogenolysis. Excess glucose 6-phosphate generates lactate (glycolytic pathway) and UA (pentose phosphate pathway). Furthermore, degradation of purine nucleotides increase UA levels. Hyperuricaemia results from excessive UA production and impaired UA renal excretion (Chen YT 2001; Glycogen Storage Disease Type I 2006).

Familial juvenile hereditary nephropathy (FJHN) (OMIM 162000) is characterized by hyperuricaemia due to severely impaired urinary excretion of urate. Uromodulin is the most abundant protein in normal human urine. Mutations in the *UMOD* gene, which codes for uromodulin, seem to be the most common cause of FJHN (Devuyst et al 2005). Hyperuricaemia and gout may appear in multiple members of a family, early in life, in association with hypertension and progressive renal impairment (Becker 2001).

Other inherited defects of glomerular or tubular function, with variable manifestations, may also present with hypouricosuria and hyperuricaemia.

Data pertinent to the pattern 'hypouricosuria (UA) U↓ and hyperuricaemia (UA) P↑' can be found in Table 3. In addition, a number of diseases, clinical conditions and situations resulting from diet and/or drug intake may present with hypouricosuria and hyperuricaemia as listed below.

UA overproduction

Sickle cell anaemia: Enhanced cell and nucleic acid breakdown. Red blood cells dehydrated an sickle-shaped (Fahlen and Agraharkar 2007; Weatherall et al 2001).

Alcoholic cirrhosis (ethanol-induced): Accelerated metabolism enhances UA production. Dehydration, ketonaemia and lactic acidaemia reduce UA excretion (Becker 2001; Lieber 1997; Qazi and Lohr 2005).

Strenuous exercise: Muscle hypoxia; increased ATP degradation. Lactic acidaemia; dehydration (Emmerson 1996; Pittman and Bross 1999; Qazi and Lohr 2005).

UA underexcretion

Decreased glomerular filtration

Chronic renal failure: Progressive and irreversible decline of UA glomerular filtration rate (Becker 2001; Qazi and Lohr 2005).

Dehydration; diabetes insipidus: Increased UA tubular reabsorption. Extracellular volume depletion (Becker 2001; Moses 2007; Pittman and Bross 1999; Qazi and Lohr 2005).

Decreased UA tubular secretion (elevated levels of acetoacetate, β-hydroxybutyrate, lactate)

Starvation ketoacidosis; diabetic ketoacidosis; lactic acidosis (tissue hypoxia): Inhibition of urate secretion by accumulated lactate and ketone bodies (regular

Table 3 Hypouricosuria (UA)↓ and hyperuricaemia (UA)↑—hereditary disorders associated secondarily with decreased uric acid (UA) clearance

UA (U)	UA (P)	Disorders	Enzymes	Comments	Manifestations	Inheritance	References
↓ 80% or more patients	↑ or N	Primary hyperuricemia–idiopathic gout	—	Biochemically and genetically heterogeneous; metabolic basis for gout remains uncertain Deficit in renal UA excretion is the major mechanism leading to hyperuricaemia	Symptoms in a minority of hyperuricaemic persons and only after 20–30 years of sustained hyperuricemia Recurrent attacks of acute inflammatory arthritis, tophus formation, urate and UA nephropathies, crystal deposits, UA lithiasis	Multiple genetic determinants	a, b, c
↓	↑	Glycogenosis I (von Gierke, GSD I)	G-6-Pase	Pentose pathway stimulated, due to G-6-Pase deficiency. UA overproduction, but impaired renal UA excretion, owing to ketonaemia and lactic acidaemia	Neonatal: lactic acidaemia, hypoglycaemia Later: hyperuricaemia, hepatomegaly, hypoglycaemic seizures, hyperlipidaemia, milky plasma (triglycerides), short stature, sometimes doll face	Autosomal recessive	a, d, e, f
↓	↑	Familial juvenile hyperuricaemic nephropathy (FJHN)	—	Severely impaired renal UA excretion Mutations in the UMOD gene seem to be the most common cause; abnormal protein accumulates in renal tubules	Hyperuricaemia and gout appear early in life in several members of a family Young women and men, children: hypertension, gout, rapid progressive renal insufficiency Sometimes: renal stones, renal failure	Autosomal dominant	a, g, h, i, j
↓	↑	Inherited defects of glomerular or tubular function	—	Undefined	Variable	—	a

↑=increased; ↓=decreased. GSD=glycogen storage disease; G-6-Pase=glucose-6-phosphatase; UMOD=uromodulin.
References: (a) Becker (2001), (b) Emmerson (2005), (c) Pittman and Bross (1999), (d) Moses (2007), (e) Perlmutter et al (2002), (f) Chen (2001), (g) Simmonds et al (1997), (h) Van Gennip (1999), (i) Qazi and Lohr (2005), (j) Devuyst et al (2005).

theory) or stimulation of urate reabsorption according to recent theories (Emmerson 1996; Moses 2007; Pittman and Bross 1999; Qazi and Lohr 2005; Roch-Ramel and Guisan 1999).

Pre-eclampsia, eclampsia: Elevated UA in plasma may be a key clue to diagnosis. Decreased renal blood flow (Fahlen and Agraharkar 2007; Kang et al 2004; Pittman and Bross 1999; Qazi and Lohr 2005).

Miscellaneous

Underexcretion of UA: May be idiopathic, genetic or acquired (intrinsic renal disease, drugs, metabolites). Sometimes UA in plasma is normal (Emmerson 1996).

Polycystic kidney disease: Hyperuricaemia and gouty arthritis precede development of renal failure. Manifestations may be renal (e.g. hypertension) and extra-renal (e.g. liver cysts) (Becker 2001; Fick and Gabow 1994; Pittman and Bross 1999).

Table 4 Hypouricosuria (UA)↓ and hypouricaemia (UA)↓—purine inborn errors of metabolism with decreased uric acid (UA) production

UA (U)	UA (P)	Disorders	Enzymes	Comments	Manifestations	Inheritance	References
↓ N*	↓ N*	PNP deficiency	PNP	T-cell immunodeficiency Autoimmune disorders are common (e.g. autoimmune haemolytic anaemia) Extremely low PNP enzymatic activity in red blood cell lysates	Profound lymphopenia and recurrent infections First years: otitis, sinusitis, pharyngitis, urinary infections, varicella More than half of children: neurological abnormalities (mental/motor retardation, ataxia, hyper/hypotonia)	Autosomal recessive	a, b, c, d, e
↓	↓	Classic xanthinuria type I	XDH (XO)	Isolated deficiency of XDH Genetic or severe liver damage High renal clearance of Xa accounts for modest elevation in plasma Patients can metabolize allopurinol	Xanthinuria, renal Xa lithiasis, irritability, acute renal failure, haematuria, urinary infection, arthritis, intestinal disturbance, myopathy, sometimes mental retardation	Autosomal recessive or acquired	a, f, g, h
↓	↓	Classic xanthinuria type II	XDH (XO), AOX	Deficiency of two enzymes: XDH and AOX Patients cannot metabolize allopurinol	Same as above	Autosomal recessive	a, g, h
↓ N*	↓ N*	Xanthinuria type III: molybdenum cofactor deficiency	XDH, AOX, SO	Defective synthesis of molybdenum cofactor, essential for the function of the 3 distinct enzymes	Neonatal: intractable seizures, ocular lens dislocation, severe neurological abnormalities; sometimes microcephaly, mental retardation Late presentation: mild symptoms	Autosomal recessive	a, h, c, i

N=normal, * late presentation; ↓=decreased; PNP=purine nucleoside phosphorylase; XDH=xanthine dehydrogenase; XO=xanthine oxidase; Xa=xanthine; AOX=aldehyde oxidase; SO=sulfite oxidase.
References: (a) Simmonds et al (1997), (b) Van Gennip (1999), (c) Simmonds and Van Gennip (2002), (d) Hershfield and Mitchell (2001), (e) Baguette et al (2002), (f) Mayaudon et al (1998), (g) Fathallah-Shaykh and Diven (2006), (h) Raivio et al (2001), (i) Johnson and Duran (2001).

Bartter syndrome: A renal tubulopathy. Hyperuricaemia (impaired UA clearance) in about 50% of patients (Bettinelli et al 1998; Devarajan and Imam 2006; Moses 2007).

Sarcoidosis: Decreased renal blood flow reduces UA clearance (Newman et al 1997; Pittman and Bross 1999; Sarcoidosis, The Merck Manual of Diagnosis and Therapy 2006).

Hypothyroidism: High prevalence of hyperuricaemia and gout in hypothyroid patients. Decreased renal plasma flow; impaired glomerular filtration (Giordano et al 2001; Pittman and Bross 1999; Yokogoshi and Saito 1996).

Hyperparathyroidism: Long-standing hyperparathyroidism: renal effects, bone resorption (Pittman and Bross 1999; Westerdahl et al 2001).

Lead intoxication: Occupational exposure or consumption of beverages from lead-containing stills. An undefined renal defect appears to underlie the hyperuricaemia. May be aetiological in patients with primary gout. Another toxic metal: beryllium (Moses 2007; Pittman and Bross 1999; Qazi and Lohr 2005).

Down syndrome: Hyperuricaemia may result from increased *de novo* purine synthesis (three required enzymes derive from chromosome 21). Some authors: UA excretion increased (Malaga et al 2005; Nagyova et al 2000; Peeters et al 1993; Qazi and Lohr 2005).

Bacterial contamination in the collecting bottle can cause degradation of UA, resulting in decreased levels in urine (Duran 2002).

Disorders associated with hyperuricaemia—frequent coexistence

Hypertension: Hyperuricaemia in 25% of untreated hypertensive subjects. UA may have a pathogenic role in hypertension (Feig and Johnson 2003; Johnson et al 2003; Moses 2007; Pittman and Bross 1999).

Insulin resistance syndrome (metabolic syndrome, syndrome X): Characterized by hypertension, abdominal obesity, hypertriglyceridaemia, hyperinsulinaemia, diabetes, reduced HDL, cholesterol and hyperuricaemia (Becker 2001; Hayden and Tyagi 2004; Johnson et al 2003).

Atherosclerosis: Hyperuricaemia may have both beneficial and detrimental actions; existence of an antioxidant–pro-oxidant urate redox shuttle (Hayden and Tyagi 2004; Johnson et al 2003; Waring et al 2004).

Acute coronary syndromes: Possibly UA has no causal role. Apparent relation: probably due to the association with other risk factors (obesity, hypertension, others) (Hayden and Tyagi 2004; Johnson et al 2003; Wannamethee 2001; Wheeler et al 2005).

Hypertriglyceridaemia: Over 75% of gout patients have high triglyceride levels. Recent studies: serum UA is strongly related to serum triglycerides (Becker 2001; Conen et al 2004; Hayden and Tyagi 2004).

Obesity: Recent studies: the hormone leptin is a possible candidate for the missing link between obesity and hyperuricaemia (Bedir et al 2003; Emmerson 1996; Johnson et al 2003).

Drugs, diet

Diuretics: 75% of all diuretic-treated subjects show hyperuricaemia; enhanced UA reabsorption (Emmerson 1996; Qazi and Lohr 2005).

Laxative abuse: Decreased UA clearance (Becker 2001; Wu et al 1993).

Table 5 Purine inborn errors of metabolism with normal uric acid (UA) excretion

UA (U)	UA (P)	Disorders	Enzymes	Comments	Manifestations	Inheritance	References
N	N	ADA deficiency[a]	ADA	T-cell and B-cell immunodeficiency Identified as the metabolic basis for 20–30% of cases with recessively inherited SCID (severe combined immunodeficiency)	Profound lymphopenia Recurrent chronic, viral, fungal, protozoal and bacterial infections Frequently: persistent diarrhoea, failure to thrive, candidiasis	Autosomal recessive	a
N	N	APRT deficiency	APRT	Sometimes detected by routine analysis of urinary sediment: characteristic spherical crystals	2,8-DHA renal lithiasis, pain, haematuria, renal failure, urinary tract infection, dysuria	Autosomal recessive	a, b, c
N	N	ADSL deficiency	ADSL	Categorized as a disorder of the *de novo* biosynthesis of purine nucleotides	Neuropsychomotor retardation, epilepsy, autistic features, hypotonia	Autosomal recessive	a, d

N=normal; ADA=adenosine deaminase; APRT=adenine phosphoribosyltransferase; 2,8-DHA=2,8-dihydroxyadenine; ADSL=adenylosuccinate lyase.
References: (a) Simmonds and Van Gennip (2002), (b) Sahota et al (2001), (c) Terai et al (1995), (d) Van den Berghe and Jaeken (2001).
[a] In ADA deficiency, UA levels in plasma may sometimes be lower than the normal control range while urinary levels may also be higher (Hershfield and Mitchell 2002).

Salicylates, ciclosporin, levodopa, methoxyflurane, warfarin, ethambutol, pyrazinamide, nicotinic acid: Decreased renal urate clearance. Salicylates (low doses) and pyrazinamide inhibit urate secretion (Becker 2001; Emmerson 1996; Moses 2007; Qazi and Lohr 2005).

Ethanol abuse: Accelerated ATP catabolism enhances UA production. Dehydration, lactic acidaemia, ketonaemia: decreased UA excretion (Becker 2001; Emmerson 1996; Qazi and Lohr 2005; Roch-Ramel and Guisan 1999).

Hypouricosuria (UA) U↓ and hypouricaemia (UA) P↓

This category covers purine inborn errors of metabolism with decreased UA production, owing to deficient enzymes in the human catabolic pathway of purines. It comprises *purine nucleoside phosphorylase (PNP) deficiency* and *xanthinurias I, II and III (molybdenum cofactor deficiency)*.

In *PNP deficiency* (OMIM 164050) very low UA levels in plasma and urine are caused by the block in guanine and hypoxanthine formation from the respective nucleosides, which accumulate in urine and plasma. The block also interrupts a major salvage pathway (Fig. 1) (Hershfield and Mitchell 2001; Purine Nucleoside Phosphorylase Deficiency 2006).

In *hereditary xanthinuria type I* (OMIM 278300) the deficiency of xanthine dehydrogenase (XDH), originally categorized as xanthine oxidase (XO), which normally degrades hypoxanthine and xanthine to UA (Fig. 1), results in very low plasma and urinary levels of UA. Highly insoluble xanthine (Xa) accumulates, but not hypoxanthine (Hx), due to the recycling through a salvage pathway. However, Xa continues to accumulate, owing to the conversion of guanine to Xa by the enzyme guanase (Fig. 1). The high rate of renal clearance and low solubility in urine cause accumulation of Xa, forming crystals and radiolucent stones. Renal failure may result. Patients can metabolize allopurinol (Fathallah-Shaykh and Diven 2006; Raivio et al 2001).

Data pertinent to the pattern 'hypouricosuria (UA) U↓ and hypouricaemia (UA) P↓' can be found in Table 4. In addition, drugs may lead to hypouricosuria and hypouricaemia: *allopurinol*, a purine base analogue, impairs UA production by inhibition of the enzyme xanthine oxidase (XO) (Becker 2001; Emmerson 1996).

Normouricosuria (UA) U_N and normouricaemia (UA) P_N

This category comprises the purine IEM *Adenosine deaminase (ADA) deficiency*, *adenine phosphoribosyltransferase(APRT) deficiency* and *adenylosuccinate lyase (ADSL) deficiency*, in which UA levels in plasma and urine are normal (Purine and Pyrimidine Disorders: APRT deficiency 2006; Purine and Pyrimidine Disorders: ADA deficiency 2006). It must be observed, however, that in ADA deficiency the UA levels in plasma may sometimes be lower than normal, while in urine they may sometimes be higher (Hershfield and Mitchell 2001).

Data pertinent to the pattern 'normouricosuria (UA) U_N and normouricaemia (UA) P_N' can be found in Table 5.

Conclusions

Uric acid measures provide important clues to diagnosis. Variation of UA concentrations in urine and plasma may be an effective tool in screening for purine IEM and related diseases and clinical conditions, all of which cover a great spectrum of disorders, leading to a wealth of clinical and biochemical manifestations. In the present work, a straightforward set of parameters was assembled in a comprehensive overview, to assist in the interpretation of abnormal UA levels in urine and plasma, providing data to facilitate diagnosis.

As research continually expands and medical science is constantly changing, this overview does not intend to be definitive or complete. However, we believe that, following UA analyses, it may prove to be helpful in the interpretation of results. Early recognition of a disorder or clinical condition will be highly beneficial for the patients and their families, by permitting prompt institution of appropriate therapy, whenever available, as well as genetic counselling.

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