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Summary

Inherited disorders of tyrosine catabolism have been identified at five of the six enzymatic steps. Under normal conditions tyrosine concentrations are regulated by its synthetic enzyme (phenylalanine hydroxylase) and especially the first catabolic enzyme (tyrosine aminotransferase). Acquired or inherited deficiency of the second catabolic enzyme (4-hydroxyphenylpyruvate dioxygenase) also results in hypertyrosinemia. Tyrosine is mainly degraded in the liver but to a minor extent also in the kidney. In tyrosinemia type I, the primary defect is

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in the last enzyme of the pathway, accumulation of toxic metabolites are seen, and the hypertyrosinemia results from secondary deficiency of 4-hydroxyphenylpyruvate dioxygenase, which also is found in severe liver disease in general and in the immature liver. Generally, there is no common phenotype to the different disorders of tyrosine degradation. The occurrence of corneal and skin lesions, as seen in tyrosinemia type II, is a direct effect of high tissue tyrosine. Cognitive impairment is common in tyrosinemia type II, probably common in type III, and increasingly reported in type I. The liver and kidney diseases of tyrosinemia type I are caused by accumulation of toxic metabolites (fumarylacetoacetate and its derivatives) and can be prevented by an inhibitor (nitisinone) of tyrosine degradation at the level of 4-hydroxyphenylpyruvate dioxygenase. Whether maleylacetoacetate hydrolase that essentially gives the same metabolic features as tyrosinemia type I results in clinical features is unclear. In alkaptonuria there is no increase in tyrosine level, and the degradation of tyrosine proceeds at a normal rate to produce homogentisate. Upon oxidation, homogentisate forms reactive intermediates and pigment, which is deposited in various tissues particularly in joints and connective tissue. In hawkinsinuria, a very rare condition, data suggest that an aberrant metabolism of 4-hydroxyphenylpyruvate in some cases may lead to failure to thrive, acidosis, and excretion of a characteristic metabolite pattern.

Introduction

Hypertyrosinemia in the newborn is usually not due to inborn errors of tyrosine (Tyr) metabolism but rather to immaturity of 4-hydroxyphenylpyruvate dioxygenase (4HPD). This is called transient tyrosinemia of the premature newborn. At any age, liver dysfunction of any cause or postprandial sampling can give mildly increased Tyr levels.

Sustained isolated hypertyrosinemia is strongly suggestive of an inborn error of tyrosine degradation.

The phenotype of tyrosinemia type I (TT1) is variable, and the severity of the disease varies with age at the onset of symptoms (van Spronsen et al. 1994). Newborns detected by neonatal screening by succinylacetone (SA) in blood are clinically asymptomatic, but plasma alpha-fetoprotein (AFP) usually is already increased suggesting prenatal damage to the liver and most children have mild prolongation of coagulation tests. In non-screened patients, the most common presentation is severe liver disease or failure between 2 and 4 months of age, often preceded by a period of nonspecific failure to thrive. Typically, there is a pronounced coagulopathy with highly increased prothrombin time and sometimes thrombocytopenia, with a disproportionately moderate increase in transaminases and normal ammonia and almost normal bilirubin. Plasma AFP can be extremely high. Sepsis is not uncommon. There may be early signs of hypophosphatemic rickets secondary to renal tubulopathy. Plasma Tyr and methionine show moderate to marked increases. In later presenting patients, laboratory signs of tubulopathy and liver disease may be more impressive than the subtle clinical picture, while clinically rickets, porphyria-like neurologic crisis characterized by pain in the limbs and sometimes by paralysis resembling Guillain-Barré, or hepatic noduli that can develop into liver cancer (hepatocellular carcinoma or hepatoblastoma) can be a presenting symptom.

In comparison with the previous edition of this book (Holme and Mithcell 2014), developmental delay in TT1 is increasingly reported and in early diagnosed patients may represent an important clinical feature (van Ginkel et al. 2017a, b), with possible relations to high concentrations of Tyr and to low concentrations of phenylalanine (Phe), showing the importance—as well as the complexity—of adequate dietary management of these patients. If real eye problems (as in tyrosinemia type 2, TT2) are seen, it is believed to be related to higher Tyr concentrations rather than nitisinone itself.

So far, some patients with (mildly) increased SA concentrations appear to have a deficiency of maleylacetoacetate isomerase (MAAI) rather than FAH (Fig. 21.1), also showing that these patients do not have liver or renal failure (Yang et al. 2017).

TT2 is characterized by eye lesions (painful recurrent corneal lesions, frequently with dendritic morphology, that may be diagnosed as herpetic keratitis if the diagnosis is not suspected), skin disease (hyperkeratosis at the pressure points of palms, finger pads, and soles of the feet), and/or developmental delay or intellectual deficiency. The disorder usually presents during infancy but may become manifest at any age. Tyr concentration is grossly elevated in an otherwise normal amino acid profile.

In asymptomatic patients referred for hypertyrosinemia, discovered by neonatal screening or in the course of an investigation for another problem, it is urgent to eliminate type I disease by showing normal liver function and normal SA. After

this, the distinction between TT2 and tyrosinemia type 3 (TT3) may be difficult as Tyr level in TT2 tends to be higher, but shows considerably overlap, while organic acids with increased 4HP point at TT3. Since the concentration of blood tyrosine may be normal in some TT1, SA is the recommended biomarker to screen TTI at birth to avoid false-negative results (Stinton et al. 2017). If SA is increased, normal liver functions point at MAAI rather than FAH deficiency.

To obtain a specific diagnosis in chronically hypertyrosinemic patients without skin or eye signs, molecular testing is the approach of choice also because enzyme studies of both TT2 and TT3 require liver tissue. Today, the dietary measures are similar, but knowing the precise diagnosis also in relation to its treatment is important.

TT3 patients have been detected because of high plasma Tyr levels in an otherwise normal amino acid profile, performed in the investigation of neurological symptoms and in mental retardation or neonatal screening programs. Eye or skin lesions have not been reported, while mental retardation and epilepsy as well as vision and language problems have (Blundell et al. 2018).

Hawkinsinuria (HAWK): This rare and incompletely understood disorder is characterized by failure to thrive and acidosis in some, but clearly not all—biochemically affected—infants. No symptoms have been reported after infancy. Autosomal dominant transmission is described. Organic acids (identification of hawkinsin (2-cystenyl-1, 4-dihydroxycyclohexenylacetate)) rather than the just slightly increased Tyr in plasma will result in its diagnosis. After infancy, 4-hydroxycyclohexylacetate appears in urine in addition to hawkinsin. The condition has responded to restriction of dietary protein as well as *N*-acetyl-L-cysteine pointing at glutathione depletion (Gomez-Ospina et al. 2016).

Alkaptonuria (AKU): The earliest physical sign of AKU is abnormal darkening of urine on standing. This sign is frequently overlooked by parents and often not explored by physicians. It should lead to investigation of the excretion of homogentisate. The finding is most likely to be noticed in diapers and is typically not detectable in older patients who live in areas with modern plumbing. Symptoms like patchy grayish pigmentation of the sclera, a blue-gray aspect to the cartilage of the ear, and arthritis, most often in the hip and knee, do not appear until early adulthood, while aortic valve leakage and aorta aneurysm are problems of late adulthood. Periods of acute inflammation may resemble rheumatoid arthritis. The arthritis may be severe and disabling in middle-aged adults. Ankylosis of the lumbosacral region is common. The specific diagnosis may be suggested by radiologists who note reduced intervertebral spacing in the lumbar spine, with calcification of the intervertebral disc and marked degenerative changes in the shoulder and hip joints. Diagnosis is confirmed by identification of homogentisate in urine, often present in millimolar amounts, and DNA mutations found in the gene for 4HPD. Nitisinone has proven to be effective in preventing the formation of homogentisate (Ranganath et al. 2018). Questions to be answered are how early nitisinone needs to be started to prevent these long-term consequences and the strictness of dietary treatment.

Nomenclature

No.	Disorder	Alternative name	Abbreviation	Gene symbol	Chromosomal localization	Affected protein	OMIM no.
21.1	Tyrosinemia type I	Hepatorenal Tyrosinemia Hereditary Tyrosinemia type I Fumarylacetoacetase deficiency	TT1	*FAH*	15q25.1	Fumarylacetoacetase	276700
21.2	Tyrosinemia type II	Tyrosine aminotransferase deficiency	TT2	*TAT*	16q22.2	Tyrosine aminotransferase	276600
21.3	Tyrosinemia type III	4-hydroxyphenylpyruvate dioxygenase deficiency	TT3	*HPD*	12q24.31	4-hydroxyphenylpyruvate dioxygenase	276710
21.4	Hawkinsinuria	4-hydroxyphenylpyruvate dioxygenase change of function	HAWK	*HPD*	12q24.31	4-hydroxyphenylpyruvate hydroxylase	140350
21.5	Alkaptonuria	Homogentisate 1,2-dioxygenase deficiency	AKU	*HGD*	3q13.33	Homogentisate 1,2-dioxygenase	203500
21.6	Maleylacetoacetate isomerase deficiency		MAAI	GSTZ1	14q24.3	Maleylacetoacetate isomerase	617596

Metabolic Pathway

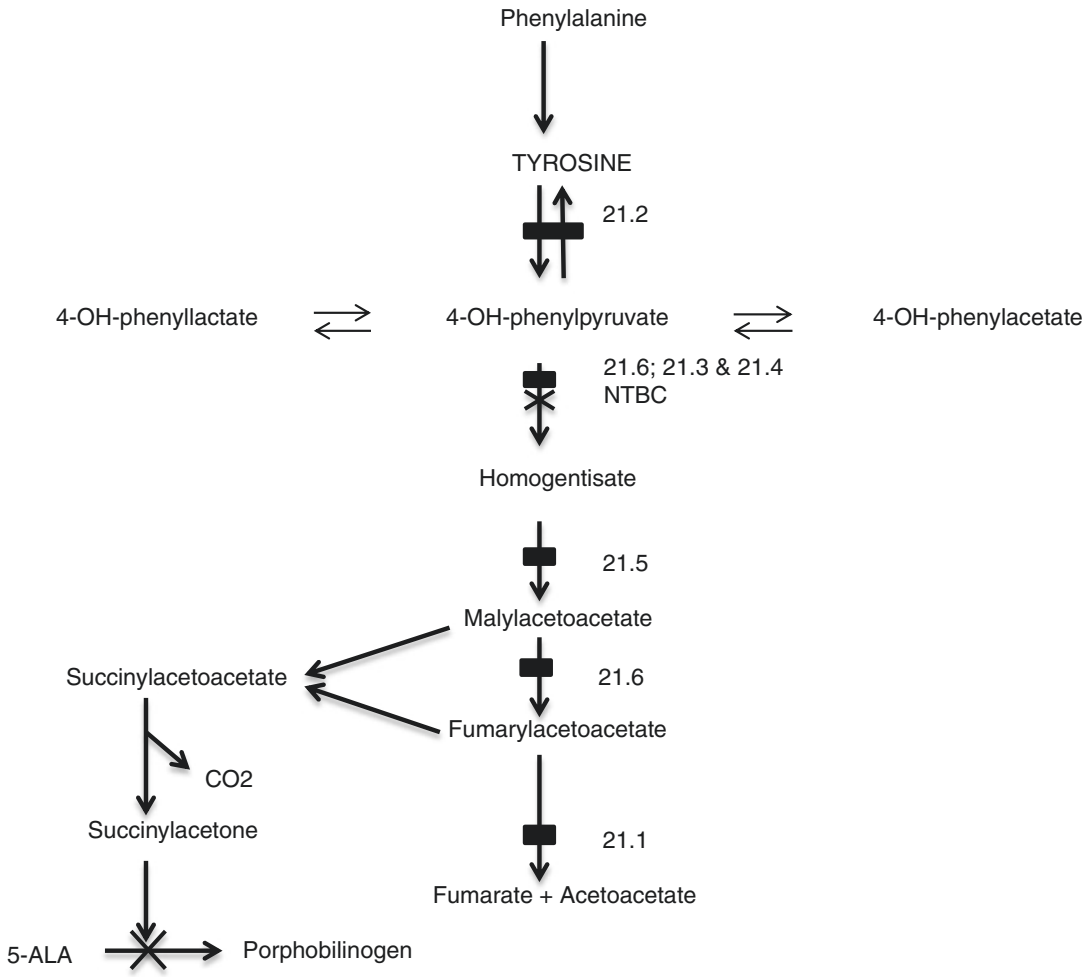

Fig. 21.1 Tyrosine degradation pathway. Diagnostically important metabolites are framed. The sites of known metabolic disorders are indicated as *filled boxes*. **21.1** fumarylacetoacetase, **21.2** tyrosine aminotransferase, **21.3** & **21.4** 4-hydroxyphenylpyruvate dioxygenase, **21.5** homogentisate dioxygenase, **21.6** maleylacetoacetate isomerase. Inhibition by succinylacetone and nitisinone (NTBC) are indicated by crosses. *5-ALA* 5-aminolevulinate

Signs and Symptoms

Table 21.1 Tyrosinemia type I

System	Symptom	Neonatal screening	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	Neurocognitive and behavioral issues	[a]	[a]	±[a]	±	±	±
	Porphyria-like neurological crisis			±	±	±	±
Digestive	Liver carcinoma[b], hepatocellular, hepatoblastoma			±	+	+	+
	Liver failure, acute		±	±			
Eye[c]	Corneal erosion				±	±	±
	Lacrimation				±	±	±
	Photophobia				±	±	±
Musculoskeletal	Rickets				±	±	±
Renal	**Hypertension**			+	+	+	+
	Nephrocalcinosis			+	+	±	±
	Renal enlargement		±	+	+		
	Renal failure, chronic						±
	Renal tubulopathy		±	+	+	+	+

Table 21.1 (continued)

System	Symptom	Neonatal screening	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Laboratory findings	4-Hydroxyphenylacetate (urine)		↑	↑	↑	↑	↑
	4-Hydroxyphenyllactate (urine)		↑	↑	↑	↑	↑
	4-Hydroxyphenylpyruvate (urine)		↑	↑	↑	↑	↑
	5-Aminolevulinic acid (urine)		↑	↑	↑	↑	↑
	Alpha-fetoprotein (serum)	↑↑	↑↑	↑↑	↑	(↑)	(↑)
	Methionine (plasma)		(↑)	(↑)	(↑)	–	–
	Porphobilinogen synthase (red blood cells)		↓		↓	↓	↓
	Succinylacetone (urine, DBS, plasma)[d]	↑/↑↑	↑	↑	↑	↑	↑
	Tyrosine (DBS, plasma)	(↑)	↑	↑	↑	↑	↑
	Phenylalanine (DBS, plasma)	n	n				

Succinylacetone is measured rapidly in order to exclude tyrosinemia type I. As measuring succinylacetone is now not that difficult anymore, measuring the decreased activity of porphobilinogen synthase activity in RBC or increased concentrations of delta-aminolevulinic acid strictly speaking is not needed anymore. Of note, increased excretion of phenolic tyrosine metabolites is present in sustained hypertyrosinemia of any cause and is of no differential diagnostic value

[a]Be aware of the risks on mental development as a result of too low Phe concentrations

[b]Lower risk in patients identified at newborn screening and treated early

[c]Higher risk in patients treated with NTBC and noncompliant with dietary treatment

[d]Succinylacetone and/or succinyl acetoacetate and/or 4-oxo-6-hydroxyheptonoate (U).

Table 21.2 Tyrosinemia type II

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Behavioral disorder		±	±	±	±
	Mental retardation		±	±	±	±
Dermatological	Blisters, erosion, hyperkeratosis on palms and soles			±	±	±
Eye	Corneal erosion		±	+	+	+
	Lacrimation		+	+	+	+
	Photophobia		±	+	+	+
Laboratory findings	4-Hydroxyphenylacetate (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	4-Hydroxyphenyllactate (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	4-Hydroxyphenylpyruvate (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	Tyrosine (DBS, plasma)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Phenylalanine (DBS, plasma)	n	n	n	n	n

Table 21.3 Tyrosinemia type III

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
CNS	Mental retardation		±	±	±	±
Laboratory findings	4-Hydroxyphenylacetic acid (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	4-Hydroxyphenyllactate (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	4-Hydroxyphenylpyruvate (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	Tyrosine (DBS, plasma)	↑↑	↑↑	↑↑	↑↑	↓↓
	Phenylalanine (DBS, plasma)	n	n	n	n	n

Table 21.4 Hawkinsinuria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Digestive	Unspecified hepatopathy		+			
Other	Failure to thrive, acidosis		+			
Laboratory findings	4-Hydroxycyclohexylacetate (urine)			↑	↑	↑
	4-Hydroxyphenylacetate (urine)		↑			
	4-Hydroxyphenyllactate (urine)		↑			
	4-Hydroxyphenylpyruvate (urine)		↑			
	5-Oxoproline (urine)		↑			
	Hawkinsin (urine)		↑	↑	↑	↑
	Tyrosine (DBS, plasma)	n	(↑)[a]	n	n	n
	Phenylalanine (DBS, plasma)	n	n	n	n	n

[a]Reported in a single patient

Table 21.5 Alkaptonuria

System	Symptom	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Cardiovascular	Mitral and aortic valvulitis					±
Dermatological	Pigmentation					±
Eye	Scleral pigmentation					+
Musculoskeletal	Arthritis					+
	Lumbosacral disc degeneration					+
	Ochronosis					+
Other	**Urine darkening on standing**	+	+	+	+	+
Special laboratory	Homogentisate (urine)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑

Table 21.6 Maleylacetoacetate isomerase deficiency

System	Symptom	Neonatal screened patients
Liver and kidney	Functions proven to be and remain normal	n
Special laboratory	Alpha-fetoprotein (serum) Succinylacetone (DBS, urine, plasma)	↑

Reference Values

Age	Phe (DBS, P)	Tyr (DBS, P)	Met (P)	SA (P and DBS)	Porphobilinogen synthase (RBC)[a]	SA (U)	5-Aminolevulinate (U)	Hawkinsin (U)	Homogentisate (U)
Years		µ mol/L			Nkat/g Hgb	Mmol/mol creatinine in random samples			
Newborn	30–120	50–150	10–60	<0.024	0.58–1.25	<0.1	<20	n.d.	<1
1–12	30–80	30–130	10–50	<0.024	0.58–1.25	<0.1	<12	n.d.	<1
>12	30–80	30–100	10–40	<0.024	0.58–1.25	<0.1	<3	n.d.	<1

[a]Enzymatic method. Reference values vary with the methodology

Pathological Values

No.	Disorder	Phe (DBS, P)	Tyr (DBS, P)	Met (DBS, P)	SA (P, DBS)	Porphobilinogen synthase activity (RBC)	SA (U)	5-Aminolevulinate (U)	Hawkinsin (U)	Homogentisate (U)
		µ mol/L				% of normal mean	mmol/mol creatinine in random samples			
21.1	Tyrosinemia I	20–200	150–1300	20–1300	0.5 to >100	1–50	0.5 to >1000	20 to >100	ND	<1-trace
21.2	Tyrosinemia II	Normal	800 to >2000	Normal	ND	Normal	ND	Normal	ND	<1
21.3	Tyrosinemia III	Normal	500–1200	Normal	ND	Normal	ND	Normal	ND	<1
21.4	Hawkinsinuria	Normal	Normal to moderate increase	Normal	ND	Normal	ND	Normal	200–2000	<1
21.5	Alkaptonuria	Normal	Normal	Normal	ND	Normal	ND	Normal	ND	>1000
21.6	Maleylacetoacetate isomerase deficiency	Normal	Normal	Normal	0.2–1.2	ND	ND	ND	ND	ND

Increased tyrosine concentration is caused by inborn or acquired deficiency of the first two enzymes of the tyrosine degradation pathway (the increased tyrosine concentration of TT1 is caused by secondary inhibition of 4-hydroxyphenylpyruvate dioxygenase by liver disease in general)

Diagnostic Flowchart in Hypertyrosinemias
(Fig. 21.2)

Fig. 21.2 Clinical and biochemical signs suggestive of hereditary tyrosinemias. *Plasma succinylacetone concentrations up to 1282 nmol/L have been reported in maleylacetoacetate isomerase deficiency

Clinical situation	Symptoms and signs	Diagnosis
Neonatal screening (Succinylacetone)	Asymptomatic Mild coagulopathy	Tyrosinemia type I if succinylacetone more than mildly increased*
	Asymptomatic No coagulopathy or liver abnormalities	Maleylacetoacetate isomerase deficiency if succinylacetone is only mildly increased*
Neonatal screening (hypertyrosinaemia)	Transaminases (±) A-Fetoprotein (+) Prothrombine time (±) Porphobilinogen synthase deficiency (+) Succinylacetone (+)	Tyrosinemia type I (tyr(P) 120-1300 µmol/L)
↘ Persistent	No liver disease Succinylcetone (-)	Tyrosinemia type II (tyr(P) 800-2000 µmol/L) Tyrosinemia type III (tyr(P) 500-1300 µmol/L) ↓ Mutation analysis (Rarely, liver enzyme assay)
Failure to thrive	Signs of liver disease (+) Succinylacetone (+)	Tyrosinemia type I
	Acidosis (+) Hawkinsin (+) 5-oxoproline (+)	Hawkinsinuria
Liver disease	Prothrombin time (+) Transaminases (±) α-Fetoprotein (+) Bilirubin (normal-100 µmol/L) Succinylacetone (U)(+)	Tyrosinemia type I
Rickets	Hypophosphatemia (+) Alkaline phosphatase (+) General aminoaciduria (+) Complete Fanconi syndrome (+) Signs of liver disease (+) Succinylacetone (U)(+)	Tyrosinemia type I
Mental retardation	Eye and/or skin symptoms (+) No other symptoms	Tyrosinemia type II Tyrosinemia type II or III

*plasma succinylacetone concentrations up to 1282 nmol/l have been reported in Maleylacetoacetate isomerase deficiency.

Specimen Collection

Test	Material	Handling	Pitfalls
Phe (Blood)	Plasma	Ambient temp	Liver disease, any cause; false negatives in treated patients
	Blood spot	Ambient temp	Variation possible due to various technical issues There are known differences with plasma >20%
Tyr (Blood)	Plasma	Ambient temp	Liver disease, any cause; false negatives in dietary treated patients
	Blood spot	Ambient temp	Variation possible due to various technical issues Not that many studies on differences with plasma
Met (P)	Plasma	Ambient temp	Liver disease, any cause
4-Hydroxyphenylpyruvate, 4-Hydroxyphenyllactate and 4-Hydroxyphenylacetate	Urine	Ambient temp	Nonspecific elevations in liver disease of any cause. Urinary levels highly variable with diet and not generally useful for patient follow-up
Succinylacetone (Blood)	Plasma	Ambient temp	Slight increase in severe liver disease; possible false positive on dichloroacetate, treatment
	Blood spot	Ambient temp	So far, succinylacetone so far seems not easy to be compared to plasma
Porphobilinogen synthase (RBC)	Heparinized blood	Ambient temp	May be close to normal in TT1 Primary deficiency of porphobilinogen synthase
Succinylacetone (U)	Urine	Ambient temp (Frozen −20 °C)	False negatives possible in dilute urine specimens with some techniques
Hawkinsin	Urine	Frozen −20 °C	Failure to recognize hawkinsin and related metabolites if the specific diagnosis is not suggested on requisition
Homogentisate	Urine	Frozen −20 °C	–
FAH activity	Fibroblasts Lymphocytes Liver	Ambient temp Frozen (−70 °C) Frozen (−70 °C)	False positive: pseudo-deficiency. False negative: back mutation with significant FAH activity in revertant areas (common in liver) Insensitivity: very low normal activity in most available extrahepatic tissues renders enzymatic diagnosis difficult
TAT activity	Liver	Frozen (−70 °C)	False positive: highly regulated enzyme with wide normal range of activity depending on physiological state
HPD activity	Liver	Frozen (−70 °C)	False positive: secondary deficiency in cirrhotic liver Late maturation prenatally; may be low in premature infants

In general plasma and urine are stored frozen until assay. Experiences of the laboratory of the late Prof Holme learned that untreated blood and urine samples retain acceptable quality if transported at ambient temperature by same day or overnight courier

Prenatal Diagnosis

DNA analysis is the preferred method for prenatal diagnosis of all diseases of tyrosine degradation. The pathogenic variation of each biological parent must be known before proposing this technique. Molecular diagnosis can be performed on cells obtained directly or by culture after amniocentesis, from chorionic villus samples or at the preimplantation stage. Measurement of SA in amniotic fluid is an acceptable approach to diagnosis of TT1 for couples in whom the causal DNA variations are not known.

DNA Testing

DNA analysis is available for all diseases of tyrosine degradation. Standard molecular diagnostic procedures can be applied, using genomic DNA of any source. If the patient comes from a background with a known ethnic founder effect or if the pathogenic variation for which he or she is at risk is known, this can be tested directly. Otherwise, exome sequencing and, if necessary, deletion/duplication analysis are the methods of choice.

Treatment and Monitoring Summary

Diet Therapy

In all forms of hypertyrosinemia but MAAI, a mainstay of treatment is dietary restriction of the intake of Tyr and its precursor Phe, plus provision of adequate amounts of other nutrients in a form that is palatable as much as possible. Close supervision is necessary in order to avoid dietary deficiencies. Compliance is an important long-term issue, especially because hypertyrosinemia itself does not directly confer a sense of discomfort. In TT1, expert consensus, without clear data, suggested that plasma Tyr should be maintained below 400 or 500 μmol/L (De Laet et al. 2013; Chinsky et al. 2017). In TT2 and TT3, the ideal levels of plasma Tyr are even less established. Eye and skin lesions have rarely been seen in TT2 patients with plasma Tyr level <800 μmol/L, suggesting that levels should be maintained below this level. However, the repeated observation of developmental delay in many TT2 patients suggests that a lower level, perhaps 400–500 μmol/L, may be more appropriate. The increasing number of studies on intellectual and executive functions as well as social abilities in TT1 has delineated that there might not only be a relation with blood Tyr but also with blood Phe concentrations (van Vliet et al. 2015; van Ginkel et al. 2017a, b) pointing at effects of low Phe and high Tyr concentrations.

The Place of Liver Transplantation in the Era Without Nitisinone and the Era with Nitisinone

In the era that only dietary treatment was available and nitisinone was not, liver transplantation was the only definitive answer to both the oncological and metabolic problem in TT1 (van Spronsen et al. 1994). This completely changed with nitisinone.

Patients presenting with liver failure usually respond favorably to nitisinone, liver transplantation only being necessary in those patients in which the liver does not respond within some 5 days or when liver failure progresses as can be seen by the increase of ammonia and bilirubin. This implies that nitisinone is an emergency treatment in infants with unexplained liver failure till TT1 has been excluded. Nitisinone is available only for oral administration. In acutely ill patients with suspected and proven TT1, all efforts should be made to administer nitisinone immediately, even not preventing from use when samples for the proof of TT1 have not yet been taken as high SA will remain present for some hours after the first dose.

The other indication for liver transplantation that still may exist is the development of liver cancer. While liver disease, acute porphyria, and renal tubulopathy are not reported anymore on adequate use of nitisinone, liver cancer can be an issue. The older the patient is at start of nitisinone, the higher the risk of pre-malignancy development in the liver till diagnosis resulting in hepatocellular carcinoma (HCC) or hepatoblastoma at presentation or later in life (Mayorandan et al. 2014; van Ginkel et al. 2017b). Patients with an AFP that does not show a normalization of AFP within some 1–2 years of nitisinone are considered to be at risk for later development of liver cancer (Koelink et al. 2006), while patients with an AFP that starts to rise again after its decrease (often not have completely normalized by optimal nitisinone use) and patients with a new nodule seen at ultrasound under nitisinone should be considered to have liver cancer necessitating immediate referral to the liver transplantation team.

Patients who have had a donor liver still show mild increased SA in both blood and urine. It has therefore been advocated to continue nitisinone after liver transplantation. However, to our knowledge, none of the patients without receiving nitisinone after liver transplantation has developed any renal cancer that theoretically could be hypothesized. At the same time, these experiments with nitisinone after liver transplantation revealed that the dose of nitisinone to diminish the SA in blood and urine in a "healthy liver" is only a fraction of the dose needed in the diseased liver in TT1 patients but at the same time may result in still higher blood Tyr concentrations, resembling the situation in AKU (Milan et al. 2017).

TT1-Nitisinone Treatment

Nitisinone combined with dietary therapy is the medical treatment of choice for patients with TT1 since 1992 (Lindstedt et al. 1992). To date, no instance of liver cancer has occurred in patients detected by neonatal screening and treated with nitisinone rapidly thereafter (Larochelle et al. 2012). Late-treated patients are at greater risk of liver cancer, but no acute episodes of liver failure or neurological crises occurred during nitisinone treatment.

Starting nitisinone in infants with liver failure is an adventure. At the one hand, these patients may still deteriorate the first days before nitisinone start to show its clinical effect (usually within 3 days), and in these patients 2 mg/kg/day might be needed. Nitisinone may increase the already increased Tyr concentrations, but the need for natural protein for anabolism probably is of more importance accepting the higher Tyr concentrations for some days if the liver accepts that amount of nitrogen load without increasing ammonia. In

that respect, attention should be paid to give clotting factors rather than fresh frozen plasma in case of too high risk of bleeding.

Starting nitisinone in patients presenting with acute intermittent porphyria caused by TT1 can also show to be very efficacious still necessitating the promotion of anabolism.

Nitisinone has a long half-life in healthy adults of 54 h, permitting once daily administration. However, the healthy situation cannot be transferred to the TT1 patient that easily as can be learned from two issues. First of all, the experiment with nitisinone in patients having or had liver transplantation learned that nitisinone metabolism is different in a healthy compared to a diseased liver. Second, a recent study showed that dividing the total daily dose into two daily doses results in better reduction of SA if compared to taking the total dose in one daily dose (Kienstra et al. 2018). That study also showed that nitisinone levels of >35 μmol/L may suffice to suppress blood SA levels to <0.6 μmol/L. The lack of total depression of SA presumably reflects a state of increased liver cancer risk. It is important to monitor dose and compliance both clinically and by repeated laboratory measurements. Therefore, the use of home sampling methods to frequently monitor not only blood Phe and Tyr but also NTBC and SA is of clinical importance. If that is not provided by the own institutional laboratory, it is advised to collaborate with metabolic institutions that provide this service.

Monitoring TT1 probably can be split into the situation with diagnosis of neonatal screening and clinical presentation, the last group of patients not only having a higher risk of liver cancer when presented after 2–3 months of age (Holme and Lindstedt 1998; Larochelle et al. 2012), but tubular function also needing longer to return to normal than the patients found by newborn screening (Maiorana et al. 2014; Maiorana and Dionisi-Vici 2017).

Therefore, in patients with clinical presentation after 2 months of age, the authors of this chapter would advise a frequency of AFP of four times a year and twice yearly ultrasound and only performing MRI (with contrast) in case of some lesion found with ultrasound if performed by an experienced radiologist, only performing yearly studies on the kidney (tubular and glomerular) when patients show some issues at diagnosis having returned to normal. In case of newborn screening, patients do even need less regular follow-up with AFP and ultrasound (twice yearly and once yearly, respectively), while kidney function measurements are only needed on clinical indication. Both groups of patients will continue to show some very mild abnormalities in prothrombin time, but this seems to be without any clinical relevance.

Instead, increased attention should be given to neurocognitive function and psychosocial development, and both parents and school teams should be aware of the risk of delay in development and behavioral issues, while research is needed in larger series to explore the adequate target concentrations of both Phe and Tyr. This at itself points to the importance of centers of expertise to centralize the experience and learn from that much faster than is being done now.

For all such patients, developmental assessment should be regularly performed, and plasma Phe and Tyr concentrations should be monitored regularly in order that evidence-based conclusions regarding development and metabolic control can be attained in the future. If developmental delay or behavioral issues are present, appropriate educational help is needed.

TT2 and TT3

These patients are offered dietary treatment as above. Cutaneous and ocular complications are usually rapidly reversed when dietary control of plasma Tyr is achieved. Symptomatic treatment can provide some immediate benefit.

It is reasonable to consider that the development delay seen in some TT2 and TT3 patients may be related to increased levels of plasma Tyr. Controlled trials in large numbers of patients are not available at present because of the rarity of these conditions and the lack of consistent documentation of outcome. This again not only asks for international cooperation in research but also for expert centers that can see as many of these patients as possible to increase and disseminate the expertise. This issue should be discussed with patients and families, and treatment should be offered accordingly. The authors treat patients with these conditions in a similar fashion to the recommendations for nitisinone-treated TT1 patients (De Laet et al. 2013).

Alkaptonuria (AKU)

Currently most treatment of AKU is still symptomatic, concentrating upon the relief of the symptoms of arthritis and joint pain. Nitisinone results in a marked reduction in homogentisate excretion at small doses of nitisinone (Milan et al. 2017). As these small doses of nitisinone for AKU imply hypertyrosinemia, dietary restriction of Phe and Tyr seems essential again. Results of long-term studies as presently undertaken will be needed to show the effect of adequate reduction of homogentisate in order to prevent the major complications of AKU. However, these studies are performed in adults not knowing whether starting nitisinone (with dietary) treatment already in infancy or childhood is more effective.

Hawkinsinuria (HAWK)

Reported patients have become asymptomatic after infancy. Patients should be given symptomatic treatment for acidosis. Temporary dietary restriction of Phe and Tyr could be considered in symptomatic patients.

Maleylacetoacetate Isomerase Deficiency (MAAI)

Reported patients are without symptoms, signs being found with mildly increased SA concentrations at newborn screening for TT1. These patients do not seem to need treatment (Yang et al. 2017).

Comments

There are six defined inborn errors of tyrosine metabolism: TT1, TT2, TT3, HAWK, AKU, and MAAI. The most common and serious of these disorders is TT1. For this disease efficient drug treatment is available with nitisinone, based on inhibition of Tyr degradation at a level prior to the formation of hepatotoxic metabolites. Early institution of nitisinone therapy is desirable, before complications occur. SA is the most sensitive and specific marker for neonatal screening of TT1, and this is now increasingly practiced in newborn screening programs. The outcome in TT1 patients detected by neonatal screening and treated early with nitisinone is very promising to date (Larochelle et al. 2012; Mayorandan et al. 2014), but attention should be focused on neurocognitive and psychosocial development in addition to liver and kidney function and porphyria-like symptoms. For TT2, dietary control of Tyr levels can prevent skin and ocular complications. Controlled dietary restriction of Phe and Tyr is a reasonable approach to all defects in the catabolism of Tyr except MAAI. Expanded newborn screening with SA efficiently detect TT1 and possibly also MAAI depending on the cut-off at newborn screening, but the other inborn errors of Tyr degradation are generally not detected by newborn screening, and a high index of suspicion by clinicians and diagnostic laboratory personnel is necessary to ensure early diagnosis and treatment.

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