12.3.3 Disorders of galactose, pentose, and pyruva

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12.3.3 Disorders of galactose, pentose, and pyruvate metabolism 2003 Yang TY, et al. (2000). Hereditary fructose intolerance presenting as Reye's-like syndrome: report of one case. Acta Paediatr Taiwan, 41, 218–20. Wasserman D, et al. (1996). Molecular analysis of the fructose transporter gene (GLUT5) in isolated fructose malabsorption. J Clin Invest, 98, 2398–402. World Health Organization (WHO) (2015). Sugars Intake for Adults and Children. WHO/NMH/NHD/15.2 (Executive summary). WHO, Geneva. 12.3.3 Disorders of galactose, pentose, and pyruvate metabolism Timothy M. Cox ESSENTIALS Inborn errors of galactose metabolism Galactose is principally found as free lactose in dairy products. Three inborn errors of galactose metabolism are recognized: Galactokinase deficiency ('galactose diabetes')—a very rare con- dition which impairs the assimilation of dietary galactose such that the free sugar and its metabolites appear in plasma and urine. Conversion of galactose to osmotically active galactitol in tissues causes premature bilateral cataracts and (occasionally) pseudotumour cerebri in infants, which are prevented by early institution of a galactose- and lactose-free diet. Classical galactosaemia (galactose-1-phosphate uridylyltransferase deficiency)—the commonest (1/47 000 births) and most important disorder. High concentrations of galactose in the plasma and tissues lead to aberrant glycosylation of glycoproteins and other glycoconjugates, including lipids. The principal manifestations are a bac- tericidal defect associated with neonatal Escherichia coli sepsis; failure to thrive; and—in older patients—growth retardation, mental retardation, renal Fanconi's syndrome, jaundice, and hepatosplenomegaly: without exclusion of lactose and galactose, death with cirrhosis is the rule. Diagnosis is made by plasma galactose, galactose 1-phosphate, and red cell transferase determinations in blood spots obtained after birth and refined by molecular

analysis of the GALT gene. Prompt institution of an appropriate diet allows survival into late adult life, but disabling cognitive and language defects and other neurological manifestations persist. Attenuated nonacute galactosaemia presents in adult life with cataracts and progressive neurological disease; premature ovarian failure is the rule in affected women. Uridine diphosphate galactose-4´-epimerase deficiency—a rare but often harmless disorder which may be identified by neonatal screening. Rarely, cataract, sensorineural deafness, and impaired psychomotor development with hepatorenal features of classical galactosaemia occur, with favourable responses to the galactose exclusion diet. Pentosuria Essential pentosuria is an asymptomatic, autosomal recessive trait affecting glucuronate metabolism, principally found in Ashkenazi Jews. Disorders of pyruvate metabolism Deficiency of the pyruvate dehydrogenase complex is the most common inherited disorder with lactic acidaemia, most often due to deficiency of the E1α subunit inherited as a dominant X-linked character. Presentation is with overwhelming neonatal acidosis; moderate lactic acidosis with progressive neurological features; or— in male children and young adults—an indolent neurological course without overt acidosis but with episodes of cerebellar ataxia induced by carbohydrate administration. Pyruvate carboxylase deficiency causes lactate/pyruvate acidosis with a necrotizing encephalopathy resembling Wernicke's encephalopathy. Hypoglycaemia may complicate intercurrent infections and starvation. Disorders of galactose metabolism Metabolism of galactose Galactose is derived from exogenous sources but constitutively de- rived de novo by metabolic interconversion from endogenous glu- cose. The chief exogenous source is the disaccharide, lactose, which is present in milk and dairy products, following the action of mu- cosal lactase in the small intestine. The concentration of lactose in human breast milk is approximately 70 g/litre (200 mM); this explains the relative sweetness of human breast milk, compared with cows' milk. Newborn infants obtain about one-fifth of their dietary energy supply in the form of galactose, which is obtained by digestion of lactose to galactose and glucose in equimolar amounts. Galactose occurs as a free sugar in certain fruits such as tomatoes and avocados, as well as legumes, brassicas, and other vegetables. It is also complexed with other molecules present in food and is a component of membrane glycoproteins, glycosamino- glycans, and glycosphingolipids abundant in nervous tissue. Assimilation of galactose from dietary sources and the de novo biosynthesis of metabolically active galactose nucleotides share reactions involving the interconversion of galactose and glucose common to the Leloir pathway. This pathway utilizes nucleoside (uri- dine) diphosphate sugar intermediates that interact with galactose 1-phosphate which directly enters mainstream carbohydrate me- tabolism (Fig. 12.3.3.1). High-energy uridine diphosphate (UDP)- sugar intermediates, especially UDP-glucose, UDP-galactose, and their nitrogen-containing derivatives such as UDP-galactosamine, are critical building blocks in the formation of glycoproteins and glycolipids, including glycosphingolipids. Intracellular concentra- tions of these metabolites reflect the activity of the Leloir pathway. The Leloir pathway employs four enzymes that catalyse essen- tial reactions for the metabolic incorporation of galactose derived from dietary sources and by de novo biosynthesis. By their actions, hexose units derived from galactose enter glycolysis, are incorp- orated into glycogen, and used for key biosynthetic processes. The enzymes are (1) galactose mutarotase—which facilitates intercon- version of the α- and β-d-galactose anomers to maintain the source of galactose in the alpha conformation necessary for its further assimilation. (2) Galactokinase—which catalyses the rapid phos- phorylation of β-d-galactose to form galactose 1-phosphate in the liver and renal proximal renal tubule. (3) Galactose 1-phosphate uridyltransferase—responsible for the conversion of galactose 1- phosphate and UDP-glucose to glucose 1-phosphate and UDP-gal- actose. (4) UDP-galactose-4´-epimerase—which reversibly catalyses

SECTION 12 Metabolic disorders 2004 regeneration of UDP-glucose and allows formation of UDP-galactose from UDP-glucose. UDP-galactose is a critical building block for the biosynthesis of essential glycoconjugates, includ ing glycosaminoglyans, glycoproteins, and glycosphingolipids. Inherited defects in the interconversion of these metabolites in- crease blood and tissue concentrations of galactose—especially when the diet contains milk or dairy products. Exogenous pathway Free galactose is released from lactose (β-d-galactopyranosyl- (1→4)-d-glucose) in the diet by the action of lactase at the intestinal brush-border membrane. Lactase preserves in the reaction products, galactose and glucose, the anomeric β-configuration of the galactose moiety in the substrate. After intestinal uptake of these monosac- charides by the sodium-dependent hexose transporter (SGLUT1), galactose enters the portal bloodstream by facilitated diffusion across the basolateral membrane via GLUT2, and this low-affinity, high-capacity transporter also brings about the uptake by hepatocytes. Metabolic incorporation of galactose occurs only as its α-d- galactose anomeric form, which is supplied by the action of the ubiquitous bidirectional enzyme, mutarotase, that maintains the conformational equilibrium of the α- and β-anomers of d-galactose. Intracellular incorporation of exogenous d-galactose that is se-lective for the α-anomer involves an endergonic reaction catalysed by galactokinase; phosphate-bond energy from ATP drives the reaction thermodynamically. After rapid phosphorylation of free galactose at the 1-carbon position to form galactose 1-phosphate, principally in the liver, the high-energy sugar nucleotide, UDP-galactose, is generated by the action of galactose-1-phosphate uridyltransferase. UDP-glucose can be regenerated by the action of UDP-galactose-4′- epimerase, which promotes flux through the Leloir pathway. De novo synthesis UDP-galactose-4′-epimerase enables the galactose moiety to be generated from glucose for the synthesis of complex glycoconjugates, providing a de novo supply of UDP-galactose that is independent of exogenous galactose from milk and other dietary components. The pathway is most active in the growing fetus. While the Leloir pathway is the main route of galactose metabolism in humans, minor pathways also operate: reduction of galactose to galactitol and oxi- dation to galactonic acid can occur, but these only partially mitigate the metabolic block at the level of the transferase that causes classic galactosaemia. A major source of endogenous galactose is the recyc- ling of galactose-containing glycosaminoglycans, glycoproteins, and glycosphingolipids in the lysosomal compartment. Galactitol appears at high concentrations in the blood and urine in classic galactosaemia, galactokinase deficiency, and epimerase defi- ciency. If the transferase is markedly deficient or absent, galactose, gal- actose 1-phosphate, galactitol, and gluconate accumulate in the tissues. Galactokinase deficiency: ‘galactose diabetes’ Failure to phosphorylate galactose in the liver and other tissues impairs its clearance from the blood so that the free sugar mainly derived from lactose in the intestine, as well as its metabolites, galactonic acid and galactitol, appear in the urine. Genetics The human gene for galactokinase maps to chromosome 17q24, with a putative second locus on chromosome 15. Numerous mutations respon- sible for galactokinase deficiency have been identified in the GALK1 gene at its chromosome 17 locus. Many of these are private, but the so- called Osaka variant, a missense mutation (p.A198V), was first identi- fied through mass neonatal screening and has a prevalence of 4.1% in Japanese individuals and 2.8% in Koreans; it is uncommon among indi- viduals of Taiwanese and Chinese ancestry. The Osaka GALK1 variant has been reported to occur in 7.8% of Japanese adults with bilateral cata- racts, in whom it may represent a true population risk factor. Homozygous deficiency of galactokinase is exceptionally rare, occurring with an approximate frequency of 1 in 1 000 000 live births. However, galactokinase deficiency occurs in East central Europe with a high incidence among the Roma (‘Gypsies’), in whom a founder Romani GALK1 mutation, p.P28T, has been found in Spain, Bulgaria,

Bosnia and Hungary. The carrier frequency in these groups is about 1 in 50, predicting a birth frequency of about 1 in 10 000 and justifying institution of a screening programme that is culturally acceptable to and actionable within this population group. Clinical features Precocious formation of cataracts in infants and children is charac- teristic, and some heterozygotes develop cataracts before the age of 40 years. When blood concentrations are high, galactose is taken up by the lens and converted to the end product, the sugar alcohol, galactitol, by the action of aldose reductase: subsequent toxic or osmotic effects lead to swelling and irreversible damage to lens fibres. Several infants have presented with benign intracranial hypertension (pseudotumour cerebri), possibly as a result of comparable osmotic effects of galactitol in the brain. Patients with galactokinase deficiency persistently excrete reducing sugar in their urine, but, apart from possible confusion with diabetes mellitus, this has no apparent significance. Dietary lactose Galactose Glucose Galactose 1-phosphate UDP-glucose UDP-galactose Glucose 1-phosphate Galactose 1-phosphate uridyltransferase Galactokinase UDP 4-epimerase Glycogen Glucose 6-phosphate Intestinal lactase Fig. 12.3.3.1 Galactose metabolism.

12.3.3 Disorders of galactose, pentose, and pyruvate metabolism 2005 Diagnosis and treatment Galactokinase deficiency should be suspected in infants or chil- dren with cataracts, and ideally reducing sugar (which will not react with glucose oxidase test strips) should be sought in the urine. Definitive diagnosis is by enzymatic assay of galactokinase in erythrocytes or cultured fibroblasts, which differentiates the dis- order from classic galactosaemia and hypergalactosaemia due to vascular disease in the liver. In populations with newborn surveillance for high blood gal- actose concentration, the deficiency may be detected as a result of finding an abnormal blood galactose concentration with normal transferase and epimerase activities. Definitive enzymatic meas- urements can be conducted on amniocytes and cultured skin fibro- blasts. Neonatal screening that depends on tests for galactose in the blood will not detect galactokinase deficiency. Lifelong treatment with a lactose- and galactose-exclusion diet prevents cataract formation, and early cataract formation in infants may even be reversed; otherwise surgical removal may be required. Urinary galactitol concentrations, which have been reported to ex- ceed 2500 mmol/mol creatinine, fall to within the reference range for healthy subjects (<3 mmol/mol creatinine) after some weeks of dietary treatment. Although there are numerous reports of bilateral cataracts in heterozygotes for galactokinase deficiency, it remains unclear whether any propensity to cataract formation in later life is prevented by dietary restriction; some authors have suggested that cataracts are more fre- quent in otherwise healthy individuals who consume abundant dairy products, but have no galactokinase deficiency. In the face of this con- troversy, it appears to be most prudent to recommend modest restric- tion of lactose intake in heterozygotes for galactokinase deficiency. Galactose-1-phosphate uridyltransferase deficiency: galactosaemia Unlike individuals in whom galactokinase is deficient, when patients who lack galactose-1-phosphate uridyltransferase ingest lactose, there is a significant rise in intracellular galactose 1-phosphate as well as blood galactose concentrations. The severe consequences of classic galactosaemia are attributed to the toxic effects of galactose 1- phosphate, principally in the liver, proximal renal tubule, and brain. Three main forms of galactosaemia are readily recognized: they may be termed classical, adult (variant), and mild—most pa- tients present in the neonatal period with the classical variant. Increasingly, patients with strongly predictive galactose-1-phos- phate uridyltransferase deficiency, enzymology and/or GALT geno- type for this acute disease are identified by neonatal screening. Genetics Galactosaemia is transmitted as an autosomal recessive trait with an overall estimated frequency of 1 in 47 000 in liveborn infants. It is more frequent in some isolated groups, most notably in the

modern Traveller population of Ireland, where there is a birth fre- quency of 1 in 480 compared with 1 in 30 000 in the non-Traveller Irish population. In African American patients from the United States of America, a relatively mild disorder has been reported that is probably due to an unstable enzyme variant; uridylyltransferase activity is absent from the red cells of these patients but amounts to some 10% of normal in samples of liver and small intestinal tissue. Patients with the so-called Duarte variant possess about one-half of the normal enzyme activity in erythrocytes but remain asymptom- atic; premature ovarian failure does not occur in women harbouring this variant. Galactosaemia is rare in Japan. The human galactosyl-1-phosphate uridylyltransferase gene, GALT, maps to human chromosome 9p13 and encodes a protein of molecular weight 43 kDa, which exists as a functional homodimer. Molecular analysis indicates that most patients with classic galactosaemia har- bour missense-type mutations and are compound heterozygotes. Numerous variant transferase enzymes are known, and more than 330 disease-associated mutations are reported. There are several wide- spread mutations: p.Q188R accounts for about two-thirds of mutant alleles in white Europeans, with a strong North-West dominance, and greater than 90% of mutant alleles in patients from Ireland. In Eastern and Central Europe, the mutant GALT p.K285N accounts for about for 30% of galactosaemic alleles and has a strong association popula- tions of Slavic origin. The so-called Duarte transferase mutation that is most frequent in persons of African ancestry has been identified as p.N314D. Molecular analysis of the transferase gene, GALT, now renders prenatal diagnosis of at-risk pregnancies possible. Pathogenesis Although the exact mechanism of toxicity is unknown, the accumu- lation of galactose 1-phosphate in a milieu with depleted inorganic phosphate probably inhibits other enzymatic reactions involving phos- phorylated intermediates and may cause purine nucleotide depletion. Aldose reductase is responsible for the direct reduction of gal- actose to galactitol, which is not metabolized further in the polyol pathway and accumulates in tissues where it contributes to the pathophysiology of galactosaemia, resembling sorbitol in its ability to cause rapid-onset cataract formation, and with potential effects in the induction of cerebral oedema and pseudotumour cerebri. Sustained excess of d-galactose as well as relative deficiency or distribution of high-energy sugar nucleotides that are required for key glycosylation reactions is likely to have effects on the brain lipids and countless glycoproteins, including circulating hor- mones. It appears plausible that the deficiency of UDP-galactose will affect the biosynthesis of key galactosphingolipids by UDP- galactosylceramide transferase in neural cells. A toxic effect on the fetal ovary due to maternal hypergalactosaemia has been postulated to account for the hypergonadotropic hypo- gonadism in affected women and girls, but abnormal glycosylation of follicle-stimulating hormone and Müllerian factor have also been suggested. Clinical features Classical galactosaemia Classical galactosaemia is associated with absent or near absent galactose-1-phosphate uridyltransferase activity, and typically with the GALT p.Q188R/Q188R genotype accompanied by severe clin- ical features in the neonatal period. Affected infants nearly always appear normal at birth, but vomiting or diarrhoea, jaundice, and hepatomegaly usually occur in the first few weeks. There is failure to gain weight, spontaneous bruising, and progressive enlargement of the liver. Cataracts may be apparent at 1 month of age, by which time abdominal distension with ascites has developed. Pseudotumour cerebri, often presenting with prom- inent anterior fontanelle presumably related to the osmotic effects of galactitol, may be apparent shortly after birth.

 Learning difficulties do not become apparent until later in the first year of life and vary greatly in severity. Many patients with galactosaemia develop severe infections with Escherichia coli during the neonatal period: Gram-negative bacterial sepsis may be

the first indication of this disorder in young infants. A bactericidal defect in circulating leucocytes has been postulated. In adult patients after reversal of the acute galactose toxicity syndrome, the most obvious sequelae are growth failure, neurological deficit, and, in women, pri- mary ovarian failure with infertility. A few patients with galactosaemia remain asymptomatic while ingesting milk, but eventually fail to gain weight. Such patients may come to light during childhood or even adult life with varying degrees of learning difficulties and cataracts. Hepatomegaly and intermittent galactosuria are usually present, and often there is a his- tory of feeding difficulties on institution of modified formula feeds during the neonatal period. The neurological manifestations of classic galactosaemia are highly variable but, despite prompt institution of dietary therapy, a degree of intellectual disability is common in affected children and adults. Characteristic learning difficulties in mathematics and spa- tial relationships with behavioural deficits have been observed, and children with galactosaemia have a particularly high risk for lan- guage impairment. Neurological manifestations, despite induction of a galactose-free diet, can include seizures, apraxia, extrapyram- idal disorders with tremor and dystonia, and cerebellar deficits. Histological examination of the brain shows nonspecific signs of in- jury with gliosis and Purkinje cell loss in the cerebellum. Serum tests of liver function are nonspecifically deranged but histological examination of the liver shows lobular fibrosis, fatty change, bile ductular proliferation, and progression to frank cir- rhosis. Involvement of the proximal renal tubule is shown by gen- eralized aminoaciduria and occasionally a full-blown Fanconi's syndrome with vacuolation of tubular epithelial cells. Follow-up studies of female patients with galactosaemia have shown a high incidence of gonadal failure with ovarian atrophy. Although this complication appears to be more common in patients in whom dietary therapy was delayed, no clear cause-and-effect relationship has been established. Men with galactosaemia have been reported to have a higher than expected prevalence of cryptorchidism and low semen volumes, but the specificity of these findings in patients with this chronic metabolic disease is unclear. In the clear-cut case of women and adolescent females, hypogonadism and premature ovarian failure has more obvious effects on health, well-being, and potential parental fulfilment. However, pregnancies occur in a few women with classic galactosaemia and usually result in the birth of healthy infants with no evidence of teratogenic effects. Lactation and breastfeeding pro- ceed normally. Since most females develop premature ovarian failure with hypergonadotropic hypogonadism, the hypogonadism and the imposed nutritional factors for metabolic control contribute to osteo- porosis, which occurs at high frequency, even in young adults. Adult or variant galactosaemia Adult or variant galactosaemia is a relatively indolent but important disease that often defies prompt conventional diagnosis. Residual galactose-1-phosphate uridyltransferase activity (c.10% of healthy reference mean) is detectable and the homozygous GALT p.S135L/ S135L missense mutation is typically present. The condition presents with neurological disease and early cataracts; hepatomegaly is not prominent and decompensated liver disease does not occur. About 85% of women with this condition have premature ovarian failure reflected in delayed menarche, amenorrhoea, oligomenorrhoea, and/or secondary amenorrhoea/premature menopause. Mild galactosaemia Mild, or biochemical, galactosaemia arises from biochemical screening in at-risk or targeted populations: the subjects harbour GALT mutations with modest effects on galactose-1-phosphate uridyltransferase activity and/or stability (c.25%), of which the com- pound heterozygous genotype, p.N314D/Q188R, the so-called Duarte 2 variant, is characteristic. These individuals are asymptomatic. Diagnosis Recognition of hereditary galactosaemia in early infancy is of paramount importance since the acute effects of galactose poi- soning may be reversed by the institution of a lactose-exclusion diet. Nearly all infants with classic galactosaemia or clinical variant galactosaemia can be identified in newborn screening that

includes testing for galactosaemia. However, clinical variant galactosaemia may be missed if total blood galactose is analysed without deter- mining red cell transferase activity. Definitive diagnosis relies on the determination of galactose- 1-phosphate uridylyltransferase activity and other galactose- metabolizing enzymes in red cells, skin fibroblasts, or leucocytes by means of a specific enzymatic assay. This procedure is required to confirm the results of initial screening tests conducted on dried blood spots (Beutler assay). The transferase activity in patients with classic galactosaemia is generally less than 1% of the normal reference range. In classical galactosaemia, red cell galactose-1- phosphate is usually greater than 0.4 mmol/litre (10 mg/dL) and red cell transferase activity is absent or just detectable. It is important to realize that in many patients with attenuated (‘mild’ or asymptomatic) clinical variants of galactosaemia, trans- ferase activity is much higher in brain and intestinal tissue (c.10% of healthy reference values), even though it may be absent or barely detectable in the red cell assay. Individuals with attenuated, clin- ical variant galactosaemia may have erythrocyte activity close to or above 1% of reference values, but very rarely greater than 15%. Reliable enzymatic or genetic testing for heterozygotes can be conducted in the parents of a child who died before the diagnosis was confirmed. In particular populations, neonatal screening for elevated blood galactose and galactose-1-phosphate concentra- tions is carried out routinely. Molecular analysis of the GALT gene encoding galactose-1-phosphate uridylyltransferase in at-risk preg- nancies is useful and can usually be requested for advising affected families (see following ‘Pregnancy’ subsection). Differential diagnosis Hereditary fructose intolerance and hereditary tyrosinaemia type 1 are credible differential diagnoses in infants and young children with the acute, classical form of galactosaemia. Transient galactosaemia with mixed glycosuria also occurs in the Fanconi–Bickel syn- drome, now known to be due to biallelic mutations in the GLUT2 glucose–galactose carrier, which is the facilitative glucose trans- porter in hepatocytes, pancreatic β-cells, enterocytes, and proximal renal tubular cells. Studies in infants have shown that persistent hypergalactosaemia can also be explained by portosystemic venous

 shunts that are often associated with patent ductus venosus or other congenital vascular abnormalities in the liver. Doppler ultrasonog- raphy is a convenient noninvasive investigation to search for such shunts. Treatment Without strict dietary treatment, most patients with classical galactosaemia die in early infancy, although some may survive with liver disease and learning difficulties beyond childhood. The course of galactosaemia is strikingly altered on withdrawal of lactose (and galactose), although the outcome of neurological disease is often disappointing and it appears that the galactose-free diet fails to confer benefit on mental development when instituted beyond the age of 2 years. An international guideline was set out in 2017 with practical recommendations for the management and follow-up of patients with this disease. Dietary exclusion Lactose is present in many nondairy foods, hence advice from an experienced dietician, as well as meticulous attention to detail, is required to eliminate it satisfactorily. Free galactose is found in fruits and vegetables, especially avocados, peas and beans, as well as other legumes. In infants, soybean milks or commercial casein hydrolysates are used as milk substitutes, and therapy is monitored by periodic assay of red cell galactose-1-phosphate concentrations. Soya milk contains galactose equivalents complexed to other mol- ecules (about 15 mg/litre) and there is a trend to adopt a completely galactose-free artificial formula in the treatment of affected infants, but there is no proof that this biochemically successful strategy in- duces better long-term outcomes. To avoid other potential vegetable sources of bound galactose in complex oligosaccharides is challenging and of uncertain value. However, even with high fruit and vegetable consumption, daily ex- posure to galactose from such

sources is unlikely to exceed 70 mg (<0.4 mmol). This compares with the endogenous daily de novo syn- thesis of galactose in healthy adults, which approaches 6 mmol (1 g). A comprehensive retrospective study that examined more than 230 children and adults with classical galactosaemia found no as- sociation between rigorous nondairy galactose restriction in early childhood and five key long-term outcomes. It thus appears un- necessary to take an extreme view of dietary measures and forbid fruit and vegetable intake once recovery from metabolic decompen- sation has occurred. Lifelong adherence to the exclusion of lactose and foods con- taining free galactose should be advocated. However, after challenge studies conducted in the Netherlands, the United Kingdom, and elsewhere, avoidance of fruits and vegetables is no longer standard practice. Monitoring metabolic control In the untreated state, the concentration of red cell galactose 1-phosphate is above 5 mmol/litre, but with close adherence to the diet it falls within a few months to less than 0.25 mmol/litre. Although biochemical monitoring has not been shown closely to predict out- comes, as a rule, expert centres recommend that the desired long- term target for blood galactose-1-phosphate concentrations should be about 0.15 mmol/litre of erythrocytes; monitoring two to three times per year in the first decade is usually practised. Management of complications Hypogonadism is a considerable problem for young girls and women with galactosaemia: it affects self-perception, physical devel- opment, life quality, self-confidence—and where relevant—family life and expectations. Most women with galactosaemia develop oligomenorrhoea and secondary amenorrhea within a few years of their first period. In one series, only 5 out of 17 women older than age 22 years had normal menstruation. Women and adolescent girls with galactosaemia benefit from the ability to discuss matters related to their reproductive health and fertility, this enable them to obtain the necessary referrals for gynaecological and endocrinological treatment with safe hormone supplementation. Review allows for regular metabolic monitoring and serial evalu- ation of bone mineralization density and vitamin D status, with opportunities to intervene where appropriate to avoid the risk of fragility fractures, particularly in women with this disease who are a great risk of osteoporosis. Pregnancy In pregnancies of heterozygous mothers who have had affected chil- dren, there is evidence that premature cataracts can be avoided in the fetus if the maternal intake of lactose is restricted. In late preg- nancy, lactosaemia and lactosuria are common findings and result from the physiological induction of lactose biosynthesis in mam- mary tissue. In rare cases, there is a potential risk of self-intoxication when women with homozygous deficiency of the transferase be- come pregnant and breastfeed, so that scrupulous dietary precau- tions are needed to maintain metabolic control during lactation. Organization of care Maintaining appropriate lifelong care for patients with galactosaemia in specialist clinics shows benefits in the provision of dietary man- agement with expert advice as well as developmental monitoring and assessment of cognitive function that is matched to educa- tional needs. Regular review in paediatric, transitional, and then adult metabolic specialist centres is critical for many patients who have overt or hidden difficulties with speech or cognition, to which should be added apraxia and the compounding effects of sensineural deafness. Prognosis The acute manifestations of galactosaemia and growth failure re- spond quickly to dietary therapy and cataract formation is prevented; in the early phases in the neonatal period, prompt intervention can lead to complete regression of cataracts. Unfortunately, some pa- tients have significant neurological deficits despite prompt and con- scientious treatment. An international survey reported the long-term outcome in 350 patients receiving dietary therapy. The presence of ovarian failure and elevated galactose-1-phosphate concentrations in patients ap- parently ingesting no lactose or galactose emphasized the import- ance of the endogenous pathway and may also explain the emergence of neurological disease in treated patients. Several pregnancies have been reported in women with classic

galactosaemia, including subjects homozygous for the p.Q188R mu- tation. In such pregnancies, high concentrations of galactitol were found in amniotic fluid, but cord blood values were within the range found in galactosaemic patients receiving strict dietary therapy.

SECTION 12 Metabolic disorders 2008 Thus, although galactitol present in maternal plasma can traverse the placenta, it probably does not harm the heterozygous fetus. Prevention
Genetic counselling As a recessive condition, the diagnosis of galactosaemia has conse- quences for members of the affected pedigree. Appropriate genetic counselling is required. Screening
Several retrospective studies indicate that neonatal screening pre- vents early death; in one survey, 80% of patients who underwent newborn screening were diagnosed by 14 days of age, compared with only 35% of patients who were not tested but who had manifest dis- ease.
A Cochrane review in 2017 concluded that there were no ran- domized controlled studies or controlled clinical studies, published or unpublished, comparing the use of any newborn screening test to diagnose infants with galactosaemia and presenting a comparison between a screened population compared with a nonscreened popu- lation. No studies of newborn screening for galactosaemia were found. However, neonatal screening for galactosaemia is available in the United States of America and in Europe, but only a small per- centage of newborns in the United Kingdom are tested. Future prospects Galactokinase inhibitors—restriction of exogenous substrate
One approach to advance this field would be to embrace the toxicity hypothesis and target the overproduction and raised intracellular concentrations of galactose 1-phosphate in classical galactosaemia. The immediate reaction target is galactokinase because this en- zyme catalyses the first committed step for the metabolic incorp- oration of α-d-galactose, upstream of the transferase in the Leloir pathway. At least one ‘lead’ candidate small-molecule inhibitor has been identified for this potential therapeutic development, but con- cerns include (a) it would in effect generate systemic galactokinase deficiency, a recognized metabolic disease; (b) this would block all acquisition of exogenous galactose and, in combination with the severe transferase deficiency, may well have unforeseen effects on the endogenous galactose pathway; (c) it would fail to address the neurological and other effects of the disease that almost certainly depend on de novo synthesis of galactose and essential biosynthetic pathways; and (d) as a kinase, galactokinase will have numerous homologies with hundreds of critical kinases affecting metabolic regulation, hence securing adequate safety and proven selectivity of any inhibitor will be a formidable challenge.
Enhancement of residual galactose-1-phosphate transferase activity Several promising small molecules that serve as potential pharma- cological chaperones have been identified, but the clinical target ex- tends beyond the liver to the brain, and the need to deliver the drug at sufficiently high concentrations to secure safe long-term efficacy after traversing the blood–brain barrier remains challenging. Gene therapy At the time of writing, investigators at Nationwide Children’s Hospital and the University of Utah have announced a stratagem based on delivering a codon-optimized version of the human galactose-1-phosphate uridylyltransferase gene to express func- tional GALT protein. Using recombinant adeno-associated viral vectors, abundant synthesis of the wild-type transferase has been obtained in cells from patients with galactosaemia. It seems likely that the clinical development of this project will involve attempts to deliver a vector with suitable tissue tropisms to allow adequate trans- duction of the liver as well as the brain, with sustained expression of the therapeutic protein sufficient to alleviate the disease. Uridine diphosphate-4′-epimerase deficiency The gene for human UDP-galactose-4′-epimerase has been mapped to chromosome 1p36–p35, and numerous mutant alleles have been identified. Epimerase deficiency is a very rare autosomal reces- sive condition that may be identified during screening for

classic galactosaemia. In most cases there are no symptoms attributable to galactosaemia, and follow-up studies have confirmed the usu- ally benign nature of this anomaly. However, a few cases of more marked deficiency of UDP-4´-epimerase have been discovered in patients otherwise manifesting the classic features of galactosaemia. The autosomal recessive nature of this inherited disorder has been confirmed by demonstrating a partial epimerase deficiency in the healthy parents of an affected infant. The condition may be con- trasted with the transferase deficiency that allows the formation of small amounts of endogenous galactose in the presence of an intact epimerase. In the absence of epimerase activity, the individual is dependent on exogenous sources of galactose, since this cannot be derived from glucose. As a complete deficiency of the epimerase would lead to an absolute lack of UDP-galactose for galactosphingolipid syn- thesis, the ingestion of very small quantities of galactose has been recommended so that brain development and biosynthesis of es- sential galactosides can proceed. Because of the dual activity of the epimerase towards UDP-acetyl glucosamine as well as UDP-glucose, it has been suggested that small supplements of the aminoacetyl gal- actosamine should also be provided. Pentosuria Pentosuria is caused by the excessive renal excretion of l-xylulose. This has no clinical significance except that it may lead to the incor- rect diagnosis of diabetes mellitus should tests for reducing sugar be carried out on the urine. Xylulose does not react with urinary test strips based on the glucose oxidase method. The disorder has historical significance as one of the five original ‘inborn errors of metabolism’ investigated by Archibald Garrod in his seminal work. Although pentosuria is a rare autosomal reces- sive trait, its frequency in Ashkenazi Jews may be as high as 0.05%. It is caused by deficiency of l-xylulose reductase, a nicotinamide adenine dinucleotide phosphate-dependent enzyme in the oxida- tive pathway of glucuronate metabolism, resulting in the daily ap- pearance of 1 to 4 g xylulose and l-arabitol in the urine. Output is continuous throughout life but greatly enhanced by the ingestion of glucuronic acid or drugs that are excreted as glucuronides. l-xylulose reductase is present in many cells including red cells and hepatocytes. Several reactions remove the carboxyl carbon atom of d-glucuronic acid to generate the pentose l-xylulose, which is

 converted to its stereoisomer, d-xylulose. d-Xylulose is phosphor- ylated to d-xylulose 5-phosphate, which can be converted to hexose phosphates in the reactions of the pentose phosphate shunt. The diagnosis is made definitively by confirming the enzymatic defect in erythrocytes, but pentosuria is most readily confirmed by paper chromatographic analysis of urine using n-butanol, ethanol, and water (50:10:40) as the partitioning solvent and orcinol- trichloroacetic acid as a detection agent; the sugar has a high mo- bility (RF 0.26) and is identified by its red colour on development. Contemporary methods of mass spectrometric analysis of urine are likely to detect the copious quantities of pentose directly and could give rise to temporary confusion in a child under investigation for unrelated illness. Long-term monitoring of 40 individuals with pentosuria over more than 16 years showed no decrease in life expectancy. Inborn errors of pyruvate metabolism The organic acids, pyruvate and lactate, are key interconvertible intermediates in energy metabolism. Pyruvate is mainly generated from glucose, but also by oxidative deamination of alanine, from the other 3-carbon amino acids, cysteine and serine, and indirectly from other amino acids. Breakdown of pyruvate proceeds by oxidation, first by pyruvate dehydrogenase, then the Krebs cycle, and finally the respiratory chain; anabolic assimilation of pyruvate is mediated by pyruvate carboxylase. Pyruvate is at the cross roads of energy metabolism: after entering the mitochondrion it generates acetyl coenzyme A and enters the Krebs cycle, by which it is oxidized. Pyruvate contributes the back- bone in the formation of amino acids including alanine, and con-

tributes critically to gluconeogenesis after the action of pyruvate carboxylase and phosphoenolpyruvate carboxykinase. Pyruvate as a source of coenzyme A is used in lipogenesis. Lactate is the product of anaerobic glycolysis and is generated en- tirely from reduction of pyruvate by lactate dehydrogenase, and it is disposed of by the reversal of this reaction. Defective metabolism of pyruvate therefore readily leads to the accumulation of lactate, the development of lactic acidaemia and the build-up of alanine. An important function of the Krebs (tricarboxylic acid) cycle is the generation of reduced nicotinamide adenine dinucleotide (NAD), which is used to generate chemical energy in the form of ATP by the action of the electron transport chain. When the metab- olism of pyruvate or the related α-ketoacid dehydrogenases in the mitochondria is disrupted, it is not surprising that the high energy- requiring tissues of nervous system are almost invariably implicated. Pyruvate dehydrogenase deficiency Deficiency of pyruvate dehydrogenase, a mitochondrial enzyme complex which generates acetyl coenzyme A from pyruvate, is the most common cause of lactic acidosis in newborn infants and chil- dren, but it is also associated with neurodegenerative syndromes in adults. Coenzyme A is one of the critical substrates for the formation of citrate and without the feed-forward delivery of pyruvate into the Krebs cycle, the cycle would be arrested and mitochondrial oxida- tive phosphorylation coupled to energy production would be mark- edly depressed. Pyruvate dehydrogenase is a multienzyme complex of five enzyme proteins: three (E1, E2, and E3) are catalytic, and two (pyruvate de- hydrogenase phosphatase and pyruvate dehydrogenase kinase) are regulatory. The combined molecular mass of the pyruvate dehydro- genase complex is about 8.5 million daltons and the complex com- prises 30 units of E1, 60 units of E2, and 6 units each of E3 and X (which is required to anchor E3 to E2). The whole complex of poly- peptides is the product of 10 distinct genes and requires three cofac- tors (thiamine pyrophosphate, lipoic acid, and coenzyme A) as well as the binding protein for one of the catalytic subunits (E3BP). The E1 catalytic protein is a heterotetramer of two α subunits and two β subunits. It is activated by dephosphorylation through the ac- tion of pyruvate dehydrogenase phosphatase and catalyses the rate- limiting reaction of pyruvate oxidation, for which it requires the activated form of thiamine (vitamin B1), thiamine pyrophosphate. Phosphorylation of the E1 complex is down-regulated by pyruvate dehydrogenase kinase, which orchestrates reciprocal allosteric con- trol of pyruvate oxidation. The second and third catalytic proteins, E2 (dihydrolipoamide S- acetyltransferase) and E3 (dihydrolipoamide dehydrogenase), are linked by co-binding to E3-binding protein and have shared func- tions and combine functionally with the Krebs cycle dehydrogenases, namely the α-ketoglutarate dehydrogenase and branched-chain α-ketoacid dehydrogenase complex. Genetics E1α-subunit mutations While all the genes that encode components of the pyruvate de- hydrogenase complex map to the nuclear genome, the most common cause of pyruvate dehydrogenase deficiency is due to mu- tations in the E1α subunit, a protein encoded on the short arm of the X chromosome (Xp22.12). Although the disease is characteristically more severe in males, manifestations in the heterozygous female are unusually frequent for an X-linked disease and probably reflect the low functional reserve of the enzyme complex in the brain and the adverse cell-intrinsic effects of lyonization in the mosaic situation. Only one-quarter of the mothers of male patients harbour a causal mutation, thus most patients arise by new germline mutations and recurrence in further offspring in the same pedigree is uncommon. Mutations in other subunits Pyruvate dehydrogenase deficiency can be caused by mutations in the E1β subunit, E1 phosphatase deficiency, E2 (dihydrolipoamide acetyltransferase deficiency), E3 (dihyrolipoamide dehydrogenase deficiency), and E3BP (E3 binding protein) Biochemical defect The pyruvate dehydrogenase complex catalyses the conversion of pyruvate to acetyl CoA within mitochondria and is rate limiting for aerobic metabolism of glucose in the brain.

Daily glucose consump- tion is 125 g in the adult brain, hence the pyruvate dehydrogenase complex is critical for brain metabolism since this is normally en- tirely dependent on the oxidative breakdown of glucose. Where the activity of the complex is impaired, accumulated pyruvate may either be reduced to lactate or transaminated to alanine, so that hyperalaninaemia and varying degrees of lactic acidaemia occur. Very rare defects in dihydrolipoyl dehydrogenase are associated

SECTION 12 Metabolic disorders 2010 with deficiency of branched-chain ketoacid dehydrogenase, pre- sumably because of the shared molecular function. Failure to carry out oxidative reactions in regions of the cortex and midbrain causes neuronal death; deficiency of four-carbon intermediates may critically impair synthesis of neurotransmitter molecules and lead to a Parkinsonian phenotype. There are three main activities associated in the complex: (1) pyru- vate dehydrogenase, a thiamine pyrophosphate-dependent complex (E1); (2) dihydrolipoyl transacetylase (E2); and (3) dihydrolipoyl dehydrogenase, a flavoprotein (E3). Also associated are a pyruvate dehydrogenase-specific kinase and phosphatase (both involved in overall metabolic regulation of the complex) as well as an es- sential lipoate-containing protein other than dihydrolipoamide transacetylase in the pyruvate dehydrogenase complex (X-lipoate), which possesses an acyl transfer function. Clinical features and prognosis The extent of clinical expression of the enzymatic defect is highly variable, but three principal patterns of pyruvate dehydrogenase complex defects are recognizable: (1) neonatal lactic acidosis, fre- quently associated with agenesis or dysgenesis of the corpus cal- losum; (2) Leigh’s encephalopathy in infants and children up to the age of 5 years; and (3) intermittent ataxia in adults. In females, mu- tations in the E1α subunit cause more homogeneous but severe dis- ease with dysmorphism, microcephaly, spastic paraplegia, and mild/ moderate cognitive impairment. There may be fulminant disease in the newborn infant: intra- uterine development is impaired, marked acidosis (blood lactate

> 10 mmol/litre) is present at birth, and the condition is rapidly fatal. In other cases, lactic acidaemia may not be apparent and the disease comes to light because of intrauterine growth failure, neo- natal hypotonia/asphyxia and feeding difficulty, and the principal abnormality is progressive psychomotor retardation often accom- panied by brainstem injury and disease of the basal ganglia. There is dysgenesis with structural abnormalities of the olivopontocerebellar tract and periventricular grey matter. Cortical atrophy and agenesis of the corpus callosum have also been reported in association with spastic quadriplegia, especially in patients presenting with neonatal acidosis. In patients who present with severe acidosis at birth, sub- acute necrotizing encephalomyelopathy of the Leigh type has been confirmed at necropsy with cystic appearances principally in the cerebral cortex, basal ganglia, and brainstem. Without intensive treatment, death usually occurs in infancy; however, should feeding by gavage be instituted, there is a protracted course with failure of neurological development, microcephaly, quadriplegia, seizures, and blindness due to the development of optic atrophy. Intermittent cerebellar ataxia or torsion dystonia have been recorded, and choreoathetoid movements occur. Peripheral neuropathy with onset in infancy has been observed.

Involuntary eye movements in children are associated with a progressively deteriorating course. E1α subunit mutations A milder form of the disorder occurs in defects of the X-linked E1α gene (PDHA1), but because pyruvate dehydrogenase deficiency is of key importance in brain metabolism, expression of disease is ob- served in females and affected males, hence this form of pyruvate de- hydrogenase complex deficiency is an X-linked dominant disorder. In boys, episodic cerebellar ataxia may be induced by feeding carbohydrate-rich foods or medicinal glucose. In these patients, some of whom are otherwise unimpaired and have normal intelli- gence, blood lactate concentrations may only be trivially elevated, and they do not normally exceed 10 mmol/litre in this condition. In contrast, in other patients a progressive brainstem disorder oc- curs, characteristic of Leigh's disease, with haemorrhagic necrosis and symmetrical spongiform appearances in the periventricular grey matter, thalami, midbrain, pons, medulla, and spinal cord; the mammillary bodies are spared. There are fascinating similarities between pyruvate dehydro- genase complex deficiency and diseases related to thiamine defi- ciency, with or without induction by exposure to alcohol (ethanol). About one-third of patients with pyruvate dehydrogenase complex deficiency have facial appearances reminiscent of the fetal syndrome due to maternal consumption of excess alcohol. This dysmorphism is characterized by a narrow head, retroussé nose, flared nostrils, and an elongated philtrum; there is frontal bossing of the skull and a broad nasal bridge. In the acquired syndrome, acetaldehyde from the maternal circulation is believed to inhibit pyruvate dehydro- genase in the fetus, and Robinson and colleagues have suggested that low endogenous activity of the pyruvate dehydrogenase com- plex due to genetic deficiency in the fetus is responsible for the de- velopmental abnormalities. A striking connection between agenesis of the corpus callosum, usually in patients with neonatal pyruvate dehydrogenase defi- ciency, has been made with the Marchiafava–Bignami syndrome, a condition characterized by degeneration of the corpus callosum and associated with longstanding abuse of alcohol. Finally, in Wernicke's encephalopathy, the effects of thiamine de- ficiency and deficiency of the pyruvate dehydrogenase complex on the brain occur principally in the regions of the greatest metabolic activity, especially in the brainstem and basal ganglia. Diminished activity of the pyruvate dehydrogenase complex is caused by thia- mine pyrophosphate deficiency, possibly combined with inhibition by the ethanol metabolite, acetaldehyde, as a plausible common factor in neuropathogenesis. Hereditary spinocerebellar degeneration appearing in early adult life has been attributed to deficiency of pyruvate dehydrogenase, but there is no direct relationship to Friedreich's ataxia. Mutations in other subunits E1β subunit Very rare patients with mutations in the E1β subunit have early-onset disease, delayed development, but moderate pro- gression of neurological disease, later with involvement of the basal ganglia and brainstem nuclei; patients with features of Leigh's syn- drome has been reported. E1 phosphatase regulatory protein Mutations in the E1 phos- phatase

> regulatory protein have been shown to cause hypotonia and feeding difficulties with psychomotor retardation, and at least one case with an acute neurological disease with lethal lactic acidosis in infancy has been described. Two mildly affected adult brothers of Turkish origin have been reported to be living in their twenties after treatment with a ketogenic diet. E2 (dihydrolipoamide acetyltransferase) deficiency E2 (dihydrolipoamide acetyltransferase) deficiency is an exception- ally rare disease, the principal manifestations of which are dystonic

12.3.3 Disorders of galactose, pentose, and pyruvate metabolism 2011 episodes together with less prominent typical features of pyruvate de- hydrogenase deficiency, such as hypotonia and ataxia. Radiological examination reveals discrete lesions restricted to the globus pallidus. E3 (dihydrolipoamide dehydrogenase) deficiency E3 (dihydrolipoamide dehydrogenase) deficiency is an autosomal re- cessive condition due to mutations in E3 dihydrolipoyl dehydro- genase, common to the action of the pyruvate dehydrogenase complex and the α-ketodehydrogenase complex and the branched- chain α-ketoacid dehydrogenase complexes. Clinical manifest- ations range from an acute disease in infants with fatal metabolic crises and decompensation associated with early-onset neurological manifestations, to isolated liver disease appearing first in adoles- cence or adult life. Hepatic decompensation, heralded by nausea and vomiting, progresses rapidly to portosystemic encephalopathy which is accompanied by coagulation failure, hypoglycaemia, and bleeding. Liver failure can result in death, even in those with late- onset disease. The biochemical defect in dihydrolipoyl dehydrogenase defi- ciency interferes with the Krebs cycle as well as the decarboxylation of pyruvate. The diagnosis is confirmed by the presence of patho- genic mutations in the DLD gene, but recently it has been proposed that the appearance of citrullinaemia is an important biomarker. A variant presentation has recently been described with a late- onset mitochondrial myopathy and limited evidence of liver dis- ease. One well-documented 19-year-old patient had lactic acidosis, a complex amino- and organic aciduria, and progressive exertional fatigue. Muscle biopsy showed mitochondrial proliferation and lack of cross-reacting dihydrolipoamide dehydrogenase. Empirical ribo- flavin supplementation induced a complete resolution of exercise intolerance with the partial restoration of the protein and resolution of pathological mitochondrial proliferation in the muscle. Oral ad- ministration of lipoic acid has been reported to correct the organic acidaemia with clinical improvement in other patients. These find- ings prompt more systematic use of all the relevant vitamin cofactors in the pyruvate dehydrogenase complex, here illustrating a classical chaperone effect elsewhere familiar in adult metabolic practice (e.g. in attenuated pyridoxine-responsive homocystinuria). E3BP (E3 binding protein) More than 20 patients with E3BP de- ficiency have been reported. It appears generally to be less severe than pyruvate dehydrogenase deficiency due to mutations in the E1α subunit. A few have shown neonatal onset with lactic acidosis, the survivors of which had a clinical course similar to the late-onset patients who suffer psychomotor retardation and encephalopathy— pyramidal spasticity, in some cases with microcephaly. Neonatal lactic acidosis is more frequent in males. For prenatal testing, diagnosis by molecular analysis of DNA is essential—and is also valuable for the identification of the other defects such as E1β- subunit deficiency. An auxiliary gene for the E1α subunit is localized as a result of retroposition from the X chromosome to the long arm of chromo- some 4, but is expressed only during spermatogenesis; its presence, however, indicates the critical

need for activity of the complex in nearly all tissues. Causal mutations in the PDHA1 gene on the X chromosome have been described; most appear to be short deletions or duplications and, at present, are not generally applicable for diag- nosis. However, analysis of X-chromosome inactivation patterns, by determination of methylation status, has proved useful for the evaluation of enzymatic assays of fibroblasts obtained from obligate carriers or female patients in whom the diagnosis is suspected. Investigation and diagnosis The diagnosis is suspected from the presence of severe acidosis at birth. It may also emerge during the investigation of neurological deficits, especially where they are associated with intrauterine growth failure. Measurement of glucose, lactate, pyruvate, 3-hydroxybutyrate, and acetoacetate in whole blood, as well as plasma amino acid concentrations, should be carried out. Hyperammonaemia with citrullinaemia, hyperlysinaemia, and hyperalaninaemia may be found. The NADH/NAD+ ratio is informative when within the healthy reference range because use of NADH is unimpaired in pyruvate dehydrogenase deficiency, whereas in respiratory electron chain defects with defective complexes I, III and IV there is an ele- vated lactate/pyruvate ratio and NADH is typically elevated. Routine screening of urine samples for organic acids may identify excessive pyruvate and lactate. Urine organic acid analysis requires the assistance of a specialized laboratory equipped for gas chro- matography, and mass spectrometry is increasingly used in major centres. Determination of lactate and pyruvate concentrations in cerebro- spinal fluid are of critical value and require special conditions for collection, transport, and storage before assay. In patients without clinically evident acidosis, cerebral disease is accompanied by striking elevations of lactate and pyruvate in the cerebrospinal fluid. Muscle biopsy for mitochondrial studies and determination of the redox state in cultured skin fibroblasts using the lactate:pyruvate ratio may also be valuable, but further specialized studies will re- quire advice from a biochemical and genetics service with experi- ence in the diagnosis of inborn errors of metabolism. Given that these measurements can show wide fluctuations in acutely ill pa- tients, several samples should be examined as recovery occurs so that the steady-state abnormalities are reflected. Glucose challenges are not critical for diagnosis, but pyruvate rises markedly in pyruvate dehydrogenase deficiency. Neuroradiological imaging reveals ventricular dilatation and cerebral atrophy. In several infant girls with pyruvate dehydrogenase deficiency, MRI showed hypoplasia of the corpus callosum as well as loss of normal white matter signal intensity. Proton magnetic resonance spectroscopy revealed high-abundance signals for brain lactate with decreased intensity of N-acetylaspartate, while phos- phorus magnetic resonance spectroscopy of skeletal muscle showed abnormally low muscle phosphorylation potentials, in keeping with the predicted biochemical disturbance. Pathological examination of previously affected siblings shows shrinkage of gyri, with involve- ment of the medulla shown by loss or hypoplasia of the pyramids. The pathological features of Wernicke’s encephalopathy may be pre- sent. The corpus callosum may be absent. Definitive diagnosis depends on genetic and enzymatic studies in skin fibroblasts or blood leucocyte samples. This should in- clude indirect measurement of the activity of the whole complex by determining release of $14CO_2$ from [1-14C pyruvate] from cul- tured cells in the presence or absence of high thiamine pyrophos- phate to explore vitamin responsiveness, and in the presence or absence of dichloroacetate which activates the enzyme in intact cells by inhibiting the regulatory E1 kinase. Mutation analysis of

 the X-linked PDHA1 gene or other PDH-related genes permits de- cisive diagnosis. While chorionic villus biopsy tissue or cultured amniocytes can be used for prenatal diagnosis, prior studies of ma- terial obtained from previously affected probands is often invaluable. Treatment Institution of a high-fat, low-carbohydrate, ketogenic diet may ameliorate

the biochemical abnormalities, but—given the degree of neurological impairment that is normally present at diagnosis— only very modest clinical improvement can be expected in those pa- tients with established disease. Therapeutic responses to the administration of high-dose thia- mine (500 mg daily) have been reported in patients with partial enzymatic deficiency, notably where ataxia and abnormal eye move- ments reminiscent of Wernicke's encephalopathy or features indica- tive of Leigh's disease are conspicuous. Dichloroacetate, which is a structural analogue of pyruvate, is an inhibitor of the regulatory E1α-subunit kinase and has been used for the treatment of primary lactic acidaemia, particularly in pa- tients with pyruvate dehydrogenase deficiency. Clinical trials in- dicate that correction of the biochemical abnormality depends on the molecular defect, and heterogeneity in patient selection may ex- plain the equivocal clinical responses observed in long- term studies. Nonetheless, dichloroacetate appears to be well tolerated and de- serves consideration in patients who fail to respond to other meas- ures, including the recommended ketogenic diets with high-dose thiamine supplementation. In patients with mutations in the multifunctional flavoprotein E3 dihydrolipoyl dehydrogenase, oral administration of lipoic acid has been reported to correct the organic acidaemia with clin- ical improvement. More striking has been the report of high-dose riboflavin supplementation in a young adult with a mitochondrial myopathy and lactic acidosis producing salutary metabolic, histo- logical, and functional reversal, plausibly due to a chaperone effect of this critical enzyme cofactor. Given the severe nature of these diseases, and in the absence of clinical trial data, there may be justification for empirical clinical use of the vitamin cofactors in selected cases. In patients with seizures, the use of sodium valproate cannot be recommended by the author: the agent is an inhibitor of mitochon- drial metabolism and has been implicated in unmasking and aggra- vating several mitochondrial diseases. Other anticonvulsants affect mitochondrial metabolism, including carbamazepine, phenytoin, oxcarbazepine, ethosuximide, zonisamide, topiramate, gabapentin, and vigabatrin. Where possible in disorders of pyruvate-driven oxidative phosphorylation, it would seem prudent to avoid these agents, but valproate probably should be avoided altogether in pa- tients with defective activity of the mitochondrial pyruvate dehydro- genase complex. Pyruvate carboxylase deficiency Inborn defects in pyruvate carboxylase, a biotin-dependent gluconeogenic enzyme, cause hypoglycaemia or profound meta- bolic acidosis with neurodegenerative features. The neuronal loss is prominent, although the enzyme is principally expressed in astro- cytes and other non-neuronal cells, suggesting impairment of the supply of nutrients derived from metabolic activity in astroglia that are essential for neuronal survival. The manifestations closely resemble those caused by deficiencies of pyruvate dehydrogenase activity and appear to be determined by the degree of residual pyru- vate carboxylase activity. Genetics This disorder is transmitted as an autosomal recessive trait. In se- verely affected patients with hyperammonaemia, pyruvate carb- oxylase protein and its mRNA are absent in the liver. A partially inactive variant enzyme is detectable in other patients. Biochemical defect Pyruvate decarboxylase is a biotin-dependent enzyme of the mito- chondrial matrix which catalyses the first step in the formation of oxaloacetate from pyruvate and carbon dioxide and is activated allo- sterically by acetyl coenzyme A. It is critical enzyme for the produc- tion of glucose by gluconeogenesis: this is achieved by carboxylation of pyruvate to form oxaloacetate, which is shuttled to the cytosol where it is acted upon by phosphoenol pyruvate carboxykinase to generate the glucose precursor phophoenolpyruvate, which is the first committed step in de novo glucose formation. Thus, in pyru- vate carboxylase deficiency, hypoglycaemia would be expected after glycogen stores are depleted. Pyruvate carboxylase as a source of lipids is explained by its intramitochondrial proximity: acetyl coenzyme A condenses with pyruvate to generate citrate. Impaired synthesis of lipids explains the often

widely distributed loss of white matter in pyruvate carboxylase deficiency. Krebs cycle intermediates may become depleted so that syn- thesis of neurotransmitters is impaired. There may also be a reduced supply of aspartate for the arginosuccinate synthase reaction of the urea cycle, hence the association with hyperammonaemia. Clinical features Three broad clinical types of pyruvate carboxylase have been recognized. Type A (infantile form) The North American form of the disease is associated the onset of vomiting, metabolic acidosis (lactate is 2–10 mmol/litre), and collapse in infants aged 2 to 6 months and associated with intercur- rent infection. The patients develop ataxia, pyramidal tract signs, and nystagmus: severe mental retardation and seizures develop rapidly. An enlarged liver is present and neuroradiological imaging shows subdural fluid, lesions resembling antenatal ischaemia-like brain lesions, and periventricular haemorrhagic cysts accom- panied by cortical atrophy. Myelination is retarded and the patient relentlessly deteriorates to die, almost always in infancy or early childhood. Type B (severe, neonatal form) The so-called French form, with severe prostration within the first 48 h of life. There is vomiting, hypotonia, lethargy, hypothermia, and rapid neurological deterioration with tremor, rigidity, poor move- ment, and abnormal ocular movements. The disease is rapidly fatal in most cases; those who survive the early days are unresponsive and die from respiratory infection before the age of 6 months. There is a marked lactate acidosis with concentrations of 10 to 20 mmol/litre (normal is <2.2 mmol/litre).

12.3.3 Disorders of galactose, pentose, and pyruvate metabolism 2013 Type C (intermittent/benign form) A rare third subtype is compatible with survival to adult life with episodic lactic acidosis and ketosis (<10 mmol/litre), these epi- sodes resolve with supportive measures and parenteral fluids. While subcortical leukodystrophy has developed in some patients, many develop normally and have cognitive ability and motor-skill devel- opment that is within the healthy reference range. Diagnosis The condition is suspected when acidosis and neurological dis- ease occur in infants, especially in the presence of hypoglycaemia. Specific diagnosis requires enzymatic assay in fibroblasts, which can also be used for carrier detection. The residual activities appear to correspond to the clinical phenotype approximately. The diagnosis can be confirmed by molecular analysis of genomic DNA for the po- tential use in case of the need for assisted reproduction when the PC gene data are hypothecated to the mother. Treatment Episodes of acidosis are treated with intravenous sodium bicar- bonate, and glucose may be required for hypoglycaemia. There is evidence that ketogenic diets containing 50% fat and 20% carbohy- drate ameliorate the biochemical disturbance and delay the onset of neurological disease. The administration of high-dose glutamate and aspartate, which may act as a source of oxaloacetate, appear to have been beneficial in some patients, at least on the composition of the plasma amino acids. Use of the anaplerotic seven-carbon triheptanoin has been de- scribed, with reports of benefit in some cases, but not all. Although biotin therapy has been disappointing in pyruvate carboxylase defi- ciency, occasional responses to high-dose lipoic acid and thiamine treatment, which may stimulate pyruvate metabolism by the de- hydrogenase complex, have been recorded. However, a collabora- tive effort to investigate their effects in selected patient groups under stratified conditions is needed. Experimental hepatic allotransplantation has been carried out in patients with pyruvate carboxylase deficiency, with salutary effects on plasma amino acids apart from glutamine, but the effect on brain function was not easy to determine in the first patient treated. FURTHER READING Inborn errors of galactose metabolism Berry GT (2000). Classic galactosemia and clinical variant galactosemia. In: Adam MP, et al. (eds). GeneReviews®. University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/books/NBK1518/ Berry GT, Walter JH (2012). Disorders of galactose metabolism. In: Saudubray J-M, van den Berghe G, Walter JH (eds) Inborn meta- bolic diseases, 5th

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