CASE REPORT

Mitochondrial Respiratory Chain Hepatopathies: Role of Liver Transplantation. A Case Series of Five Patients

Elisabeth De Greef · John Christodoulou · Ian E Alexander · Albert Shun ·
Edward V O'Loughlin · David R Thorburn · Vicki Jermyn · Michael O Stormon

Abstract Introduction: Orthotopic liver transplantation (OLT) in patients with mitochondrial respiratory chain disorders (MRCD) is controversial because of possible multi-organ involvement.

Aim: To illustrate the clinical diversity of MRCD, the difficulty in making an accurate tissue diagnosis and whether to undertake OLT in five patients with proven MRCD. A review of the reported cases in the literature is presented.

Methods: Retrospective chart review from 1995 to 2007 at a paediatric liver transplant centre where five children with hepatic MRCD were identified.

Results: Patient 1 was transplanted for 'cryptogenic' cirrhosis. The diagnosis of MRCD was made on the explant. The patient remains well 5 years after transplant. Patient 2 presented with fulminant liver failure at 3 months of age. Although no extrahepatic manifestations were identified, OLT was not considered. Patient 3 presented with recurrent hypoglycaemia and was transplanted for fulminant hepatic failure at 12 months of age. He died of pulmonary hypertension 9 months post OLT. Patient 4 was diagnosed with MRCD at the age of 2 years. Death occurred at the age of 14 years, while listed for combined liver–kidney transplant, after a stroke-like episode following severe sepsis. Patient 5 developed liver failure after valproic acid was instituted for seizures. Mitochondrial DNA depletion syndrome was diagnosed and transplantation was not offered.

Conclusion: Hepatic MRCD has a variable presentation. Diagnosis requires the measurement of respiratory chain enzymes on tissue from liver biopsy. Whether to proceed to OLT is a difficult decision given a good outcome in a minority of cases, suggesting that MRCD should not be an absolute contraindication to liver transplantation.

E.De Greef · E.V. O'Loughlin · V. Jermyn · M.O. Stormon (✉)
Department of Gastroenterology, The Children's Hospital at Westmead (CHW), Hawkesbury Road, Locked Bag 4001, Westmead 2145, NSW, Australia
e-mail: Michaes6@chw.edu.au

J. Christodoulou · I.E. Alexander
Genetic Metabolic Disorders Service, The Children's Hospital at Westmead (CHW), Hawkesbury Road, Locked Bag 4001, Westmead 2145, NSW, Australia

J. Christodoulou · I.E. Alexander · M.O. Stormon
Discipline of Paediatrics and Child Health, University of Sydney, Sydney, NSW, Australia

A. Shun · M.O. Stormon
Australian National Liver Transplant Unit (ANLTU), Royal Prince Alfred Hospital, Missenden Road, Camperdown 2050, NSW, Australia

D.R. Thorburn
Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC 3052, Australia

D.R. Thorburn
Department of Paediatrics, University of Melbourne, Melbourne, VIC 3052, Australia

Introduction

Mitochondrial respiratory chain diseases (MRCD) are disorders with multiple manifestations. Symptoms can be restricted to a single organ, but MRCD are more commonly recognised as presenting with multi-system disease especially involving muscle and the nervous system (Sokol 1999; Gillis 2003). Therapeutic options, usually unsatisfactory,

may involve a dietary approach, vitamin cofactors, and antioxidant medication (Ds 2010). The natural disease course is often progressive, affecting more organs or with increasing organ impairment. The hepatic manifestations include fulminant hepatic failure, chronic liver failure leading to end stage liver disease, and hepatocellular carcinoma (Sokol 1999; Gillis 2003; Scheers et al. 2005). Orthotopic liver transplantation (OLT) is a potential lifesaving therapy for multiple types of end stage liver disease, but in MRCD OLT is only considered if extrahepatic manifestations have been carefully excluded. We illustrate the diversity in presentation, the unpredictable disease course, the importance and difficulty of accurate tissue diagnosis, and how these factors influence the decision for OLT in five paediatric MRCD patients.

Case Reports

Patient 1 was a 6-year-old non-consanguineous Caucasian boy referred because of hepatosplenomegaly, recurrent epistaxis, loose stools, and intermittent nausea. Liver tests (LFT) showed minor liver enzyme abnormalities with preserved synthetic function (Table 1). Investigations

excluded chronic viral hepatitis, alpha-1-antitrypsin deficiency, Wilson disease, autoimmune hepatitis, congenital defects of glycosylation, and glycogen storage disease type 3. A liver biopsy done as part of these investigations did show microvesicular and macrovesicular steatosis which at that time was not thought to be of significance. He received a diagnosis of 'cryptogenic cirrhosis'. Liver transplantation was successfully performed at 13 years of age via a left lobe cut down graft because of progressive liver failure. Pathology of the explanted liver showed significant macrovesicular and microvesicular steatosis with established micronodular cirrhosis. Concerns regarding a possible MRCD were confirmed by enzymology of the explant liver showing a low level of respiratory chain complex I enzyme activity (Table 2). Five years post transplant the patient is well with no evidence of liver dysfunction. Cardiac, Ophthalmological, and cerebral MRI have demonstrated no signs of other organ involvement.

Patient 2 was a term male infant born to first cousin Pakistani parents. At 2 months he was admitted because of lethargy, feeding difficulties, weight loss, and jaundice. There was marked hepatomegaly. Liver function tests on admission showed severe synthetic dysfunction (Table 1). Serum lactate on admission was 11.4 mmol/L, ammonia

Table 1 Blood biochemistry results on presentation

	Patient 1	Patient 2	Patient 3	Patient 4		Patient 5
Bilirubin Tot/Conj (μmol/L) (1–15/1–10)	17/4	261/196	104/92	19	85/28[a]	32/17
ALT (< 45 U/L)	161	459	154	56	37[a]	162
GGT (< 50 U/L)	71	130	630	481	14[a]	81
Albumin (35–52 g/L)	43	23	27		18[a]	24
INR	1.1	6.1	1.6		3[a]	3.5
Lactate (< 2 mmol/L)		11.4	2.9	4.1	2.3[a]	6.5

[a] Results from patient 4 at second presentation at the age of 14 years

Table 2 Respiratory chain enzymes and mitochondrial DNA levels

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Normal range
Complex I	17	29	4	38	42	82–118
Complex II	119	99	170	154	200	89–120
Complex III	67	97	22	36	30	68–136
Complex IV	73	103	36	20	63	63–123
Citrate synthase	126	292	297	303	254	93–111
mtDNA/nDNA	61	53	6	130	7	66–146
Enzyme defect	I	I	I, III, IV	I, III, IV	I, III, IV	

Enzyme activities are expressed as % of control mean relative to protein. Complex I is NADH-Coenzyme Q1 oxidoreductase; Complex II is Succinate-Coenzyme Q1 oxidoreductase; Complex III is decylbenzylquinol-cytochrome c oxidoreductase; Complex IV is cytochrome c oxidase. mtDNA/nDNA is the ratio of mitochondrial DNA relative to nuclear DNA expressed as % of control mean. 'Normal Range' was determined on at least six tissue samples obtained from children lacking evidence of respiratory chain disease. Methods for enzyme and DNA analyses were as described previously (Dimmock et al. 2008; Tzoulis et al. 2006)

55 μmol/L (40–145), and creatine kinase was 42 U/L (<200). After exclusion of congenital hemochromatosis, galactosemia, tyrosinemia, congenital defects of glycosylation, and fatty acid oxidation defects (FAOD), a mitochondrial hepatopathy was strongly considered, and open liver (and muscle) biopsy with fresh frozen plasma (FFP) support was performed. Complex I enzyme activity was found to be low in the liver (Table 2) with normal levels of complexes II, III, and IV and elevated activity of the mitochondrial marker enzyme citrate synthase. Enzymology on muscle tissue was normal. The three most common European POLG mutations were absent (Hakonen et al. 2007) and there was no clear mitochondrial DNA (mtDNA) depletion. Multi-organ assessment involving cardiology, ophthalmology and neurology did not reveal any evidence of extra-hepatic MRCD. OLT was not offered because the young age and the severity of the underlying disease were considered poor prognostic factors. The patient died at the age of 3.5 months due to liver failure precipitating multi-organ failure.

Patient 3 has been previously reported (Barclay et al. 2005). Initial presentation was at 7 months of age with hypoglycaemic coma after a 24-h vomiting illness with poor oral intake. Table 1 shows the presenting biochemical profile with a mild coagulopathy. Other investigations included normal ammonia and creatine kinase and mildly elevated lactate (2.9 mmol/L, normal range 0.5–2). A fatty acid oxidation disorder was excluded by normal function in skin fibroblast studies (K Sim, Western Sydney Genetics Program, Children's Hospital at Westmead, Sydney, Australia). Open liver and muscle biopsies were performed with FFP support. Liver histology showed macrovesicular and microvesicular steatosis and an increased number of morphologically normal mitochondria on electron microscopy. Muscle histopathology was normal.

Recurrent episodes of hypoglycaemia continued despite cornstarch supplementation, and by 12 months of age liver failure developed requiring OLT. The results of respiratory chain enzyme essay (Table 2) were not available until just after transplantation, confirming the diagnosis of a severe MRCD affecting complexes I, III, and IV in the liver with normal muscle analysis. Further investigation for MRCD in other organ systems (cardiac, neurological) was normal.

Twelve months post transplantation hypoglycaemia recurred and he developed renal tubular acidosis, thought to be due to a combination of tacrolimus toxicity and MRCD. Eighteen months post transplant he had recurrent episodes of altered consciousness secondary to attacks of severe pulmonary hypertension. No known causes of pulmonary hypertension were identified, and a change in immunosuppression from tacrolimus to cyclosporine was without benefit. Despite treatment with anticoagulants, home oxygen, and diuretics, a severe pulmonary hypertensive crisis occurred at home with subsequent cardiac arrest and death.

Subsequently, the original liver biopsy showed gross mtDNA depletion (Table 2), in keeping with the high activities of Complex II and citrate synthase, which are nuclear-encoded. Sequencing of the POLG and MPV17 genes did not show any mutations. He appeared compound heterozygous for two putative splicing mutations in DGUOK.

Patient 4 has also been previously reported (Freckmann et al. 1997), a female child of unrelated Caucasian parents. Failure to thrive occurred over the first 6 months of life. She was hospitalised in the first 2 years of life due to recurrent episodes of vomiting. Significant hypoglycemia (<0.5 mmol/L, normal 2.5–5.5 mmol/L) was noted, along with raised serum lactate (4.1 mmol/L, normal < 2.0 mmol/L) with a normal pyruvate giving a lactate/pyruvate ratio of 50 (normal ratio < 25). Hepatomegaly was noted with mildly abnormal liver function tests (Table 1).

At 26 months of age liver and skeletal muscle biopsy was performed. Respiratory chain enzyme studies (Table 2) revealed severe defects of complexes I, III, and IV in the liver but normal activities in skeletal muscle. Liver DNA showed no major rearrangements of the mitochondrial genome, no evidence of mtDNA depletion and no mutations identified by sequencing the entire mtDNA genome. Profound sensorineural hearing loss had been diagnosed early in life needing a cochlear implant at the age of 2 years. Subsequent development remained normal despite progressive asymptomatic liver dysfunction.

Having been lost to follow up for several years, she presented at the age of 14 years with marked anasarca after an apparent viral illness. Her height and weight were well below the third percentile and she had hepatosplenomegaly. LFT showed synthetic dysfunction (Table 1) and renal dysfunction was also noted (creatinine 125 μmol/L, measured glomerular filtration rate 42 ml/min/1.73 m^2). She had pancytopaenia (Hb 85 g/L, WBC 3,500/μL, platelets 41,000/μL, reticulocytes 1.2%) and bone marrow aspirates from two different sites showed a moderately hypocellular marrow with the unusual features of sea blue histiocytes and foamy macrophages. Cardiac, ophthalmologic, and neurologic reviews did not show any other organ involvement. Computed tomography of her brain was normal; MRI could not be performed because of her cochlear implants. Her neurocognitive development was assessed as normal and after much debate it was decided to list her for combined liver–kidney transplantation.

Shortly after being listed, she presented with acute bacterial peritonitis and septic shock. Subsequent multi-organ failure with upper gastrointestinal haemorrhage developed, requiring ventilation, haemofiltration, and FFP support. CT scan of the brain now showed a hypodense area

in the white matter of the left posterior parietal region, suggestive of a cerebral infarct, which was confirmed by cerebral perfusion scan. Transplantation was now contra-indicated, and palliative care was instituted. Death occurred soon after withdrawal of ventilatory support.

Patient 5 was the first born child of unrelated Australian-Hungarian and Lebanese parents. Growth failure was noted at the age of 9 months and gross motor development and speech were both significantly delayed. Endocrinology evaluation for short stature was normal. Neurological investigations for ataxia, subtle left hemiplegia and ptosis of the right eye included a normal MRI of the brain and an electroencephalogram with insignificant changes. At the age of 5 years, absence-like episodes with drop attacks occurred. An electroencephalogram showed epileptic activity and she was started on valproic acid with improvement in her symptoms.

Five months later, following a viral illness, she was admitted to hospital with liver failure with a high lactate to pyruvate ratio (31, normal < 25) (Table 1). Valproic acid was ceased on admission (level 661 μmol/L, normal range 300–700) and supportive treatment was instituted.

While other aetiologies were being excluded, the combination of valproic acid induced liver failure in a developmentally delayed child raised suspicion of an underlying MRCD. An open liver and muscle biopsy with continuous FFP infusion was performed. Liver histology showed centrilobular necrosis with mild microvesicular and macrovesicular steatosis, while the muscle biopsy was normal. Respiratory chain enzymology on the liver biopsy (Table 2) was low for Complex I and Complex III, and borderline low for Complex IV. mtDNA depletion syndrome was subsequently confirmed by DNA testing. Testing for three common mutations in the POLG gene (Kirby and Thorburn 2008) indicated compound heterozygosity for two POLG missense mutations. The clinical, biochemical, enzymatic, and molecular findings were compatible with a diagnosis of Alpers–Hüttenlocher syndrome. Despite ceasing the valproate her liver function continued to deteriorate and she died. Liver transplantation was not considered because of the underlying diagnosis.

Discussion

MRCD hepatopathies can have variable clinical presentations at different ages, ranging from acute liver failure to chronic liver disease, as illustrated in this report. The liver can be the only organ affected (patient 1), can be the presenting organ (patients 2 and 3), or can be part of a multi-system disease (patient 4 and 5). MRCD usually present with neuromuscular involvement, but it should be suspected in any acute hepatic failure or in any case where two unrelated organs seem to be affected.

The presence of microvesicular steatosis in liver histology should prompt consideration of MRCD. Although not specific, the relationship between microvesicular steatosis and MRCD has been documented previously (Mandel et al. 2001). Microvesicular steatosis can also occur with other diseases causing mitochondrial dysfunction such as Wilson disease, Reye syndrome, drug toxicity, and FAOD (Mandel et al. 2001). Patient 1 had microvesicular steatosis on his first biopsy, but the significance of this finding was not appreciated at the time.

Diagnosis of MRCD by determination of enzyme activity in liver tissue is difficult in acute hepatic failure, where a liver biopsy is required in severely coagulopathic patients. The amount of tissue required for enzyme analysis is more than can be obtained by one core of either a percutaneous or a transjugular biopsy, and thus a surgical open wedge liver biopsy under direct vision has become our preferred option; FFP support is started 24 h before the procedure, continuing for at least 3–4 days afterwards. Although the procedure can destabilise the patient for 24–48 h, we have generally found this a safe and effective approach.

The diagnosis also requires an experienced metabolic service with appropriate laboratory facilities. The time taken for test results is often several weeks or longer given the highly specialised nature of the analysis, but a more rapid turnaround within 2–3 days has been possible when clinically required.

Decision making regarding OLT in patients with MRCD and liver failure is difficult. In our series three of five patients were considered ineligible for liver transplantation. In patient 2, the severity of disease and the young age implied poor outcome (Cormier-Daire et al. 1997), although no other organs were involved. The diagnosis of Alpers–Hüttenlocher syndrome in patient 5 precluded OLT (Delarue et al. 2000; Kayihan et al. 2000) and although patient 4 was listed for OLT after much deliberation, it was unclear if the stroke-like episode was due to septic shock or a consequence of the underlying MRCD. She was delisted.

The outcome post OLT in MRCD patients is less favourable than for other liver disorders. Together with our two cases, a total of 40 patients have been reported in the literature (Scheers et al. 2005; Barclay et al. 2005; Delarue et al. 2000; Kayihan et al. 2000; Mancuso et al. 2005; Dubern et al. 2001; Durand et al. 2001; Goncalves et al. 1995; Rake et al. 2000; Sokal et al. 1999; Thomson et al. 1998; Salviati et al. 2002; Rabinowitz et al. 2004; Dimmock et al. 2008; Tzoulis et al. 2006; Freisinger et al. 2006; Slama et al. 2005; Tadiboyina et al. 2005; Kaji et al. 2009) (Table 3). Nineteen patients were knowingly

Table 3 Reported experience of OLT in MRCD

Study	Age	Fulminant	Pre OLT diagnosis	Defect	Outcome	Survival
Dubern et al. (2001)	8 d	No	No	Generalised	Neuro degeneration and PHT	Death
	6 m	Yes	No	Generalised	Mild motor delay	Alive
	4 m	No	Yes	Partial C IV	MOF	Death
	3 m	No	Yes	C I and C IV	Normal, persistent acidosis	Alive
	5 m	No	Yes	C I, C III and C IV	Normal	Alive
Kayihan et al. (2000)	12 y	Yes	No	?	Neuro degeneration and RI	Death
Rake et al. (2000)	8 w	Yes	Yes	C I and C IV	Normal	Alive
Delarue et al. (2000)	3 y	Yes	No	Generalised on muscle	Neuro degeneration and RI	Death
Scheers et al. (2005)	2 m	No	Yes	C I, C III and C IV	Normal	Alive
	?	No	No	C IV	Normal	Alive
Thomson et al. (1998)	4.5 m	Yes	No	C I on muscle	Neuro degeneration and RI	Death
	4.5 m	Yes	No	Generalised muscle	Neuro degeneration and RI	Death
Goncalves et al. (1995)	3 m	No	No	C I, C III and C IV	Normal	Alive
Sokal et al. (1999)	3 m	Yes	Yes	C IV	Normal	Alive
	7 m	Yes	Yes	Generalised	Neuro degeneration and PHT	Death
	NN	Yes	Yes	CI and C IV	MOF	Death
	6 m	Yes	Yes	?	Normal	Alive
	3 m	No	Yes	?	MOF	Death
	3 m	No	Yes	?	Normal	Alive
	1 m	Yes	Yes	ND	MOF	Death
	2 m	Yes	Yes	?	Normal	Alive
Durand (2001)	< 1 y	Yes	No	??	Neuro degeneration and RI	Death
	< 1 y	Yes	No	?	Normal	Alive
	< 1 y	Yes	Yes	?	MOF	Death
	< 1 y	Yes	Yes	?	MOF	Death
	< 1 y	Yes	Yes		Mild developmental delay	Alive
Rabinowitz et al. (2004)	1 w	No	No	?	MOF	Death
Salviati et al. (2002)	6 m	No	?	C I, C III and C IV	Normal, tubulopathy	Alive
Dimmock et al. (2008)	6 w	No	No	Generalised	Neuro degeneration	Death
	7 w	No	No	Generalised	Neuro degeneration, cardiac arrest	Death
	3 m	No	No	C I, C III and C IV	Neuro degeneration	Death
Tzoulis et al. (2006)	20 y	No	?	Generalised	Epilepsy, nystagmus	Death
	19 y	No	?	Generalised	Epilepsy, ataxia	Alive
Freisinger et al. (2006)	1 y	No	Yes	Generalised	Normal	Alive
Kaji et al. (2009)	17 m	No	?	Generalised	MOF	Death
Mancuso et al. (2005)	1 y	No	Yes	C I, CII, CIII and CIV	Pulmonary hypertension and neuro degeneration	Death
Slama et al. (2005)	6 m	Yes	No	C I and C IV	Pulmonary hypertension and neuro degeneration	Death
Tadiboyina et al. (2005)	1 y	Yes	Yes	C I and C IV	Mild developmental delay	Alive
Our data	6 y	No	No	C I	Normal	Alive
	7 m	No	No	C I, C II and C IV	Hypoglycemia, tubulopathy and PHT	Death

Y years; *m* months; *w* weeks; *NN* newborn; *C* Complex; *ND* not done; *MOF* Multiple Organ Failure; *RI* Respiratory insufficiency; *PHT* Pulmonary Hypertension; ? not mentioned

transplanted with a diagnosis of MRCD already established, 17 had MRCD diagnosed post transplant, while for 4 patients no information was available. Twenty-two (55%) of the forty transplanted patients died up to 24 months post transplant. The causes of death were early postoperative multi-organ failure (8 of 22), neurologic degeneration with respiratory complications (10 of 22), and five patients with severe pulmonary hypertension. Of the 18 (45%) surviving patients followed up between 5 months and 8 years, only 3 were described as having mild developmental delay and one patient had epilepsy and ataxia. Although the numbers are small, patients diagnosed pre-transplant have a higher

survival rate post transplant than patients diagnosed post-transplant. Five of seventeen patients with a post transplant diagnosis (29%) survived, compared with 11 of 19 (58%) pre transplant diagnosis. The difficulty in selection of MRCD-related transplant candidates reflects in their overall long term post transplant survival of 44%, compared to >80% in other liver diseases (Kamath and Olthoff 2010). To optimise the outcome, exclusion of progressive extra hepatic manifestations is mandatory. Clinical evaluation for this purpose is problematic, particularly in young infants because patients may be asymptomatic early on despite multiple organ metabolic involvement. More objective evaluation as described by Munnich et al. (1996) is warranted.

Although genetic studies have shown only partial correlations between genotype and phenotype, it may be a future key factor in outcome prediction. Different mutations can give rise to the same phenotype, while different clinical phenotypes can occur with the same mutation, sometimes within families (Kirby and Thorburn 2008; Munnich et al. 1996; DiMauro and Schon 2003; Lee and Sokol 2007). Due to heteroplasmy and mitochondrial segregation in primary mtDNA disorders, clinical features may stabilise and disappear, whilst new clinical symptoms can appear (Ducluzeau et al. 2002). In nuclear encoded defects such as mtDNA depletion, symptoms usually progressively worsen. Three of four patients who died in this small cohort had a generalised respiratory chain enzyme deficiency and evidence of extrahepatic disease, with only one of them receiving a transplant (patient 3). Two patients had a complex 1 enzyme defect. One died in infancy (patient 2) without being offered transplantation, while the other was successfully transplanted before being diagnosed with a MRCD (patient 1). Genetic testing was performed in four of five patients. Patient 5 was a compound heterozygote for missense mutations in POLG. Mutations in POLG, an enzyme responsible for the repair and replication of mtDNA (Lee and Sokol 2007), are often associated with Alpers–Hüttenlocher syndrome where it has been reported to occur in up to 87% of patients with this disorder (Nguyen et al. 2006).

In summary, this small cohort reflects the wide spectrum of liver disease seen in MRCD. Children with a mitochondrial hepatopathy who require transplantation present a major management dilemma in making an accurate diagnosis, determining the extent of extrahepatic manifestations and estimating the likelihood of progression. Thorough investigations are required to determine the degree of multi-organ involvement before listing for transplantation. Hopefully, improved phenotype–genotype correlations, coupled with next generation sequencing technologies, will help us in this decision.

References

Barclay AR, Sholler G, Christodolou J, Shun A, Arbuckle S, Dorney S et al (2005) Pulmonary hypertension–a new manifestation of mitochondrial disease. J Inherit Metab Dis 28(6):1081–1089

Cormier-Daire V, Chretien D, Rustin P, Rotig A, Dubuisson C, Jacquemin E et al (1997) Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. J Pediatr 130(5):817–822

Delarue A, Paut O, Guys JM, Montfort MF, Lethel V, Roquelaure B et al (2000) Inappropriate liver transplantation in a child with Alpers-Huttenlocher syndrome misdiagnosed as valproate-induced acute liver failure. Pediatr Transplant 4(1):67–71

DiMauro S, Schon EA (2003) Mitochondrial respiratory-chain diseases. N Engl J Med 348(26):2656–2668

Dimmock DP, Zhang Q, Dionisi-Vici C, Carrozzo R, Shieh J, Tang LY et al (2008) Clinical and molecular features of mitochondrial DNA depletion due to mutations in deoxyguanosine kinase. Hum Mutat 29(2):330–331

Ds K (2010) Treatment of mitochondrial electron transport chain disorders: a review of clinical trials over the past decade. Mol Genet Metab 99(3):246–255

Dubern B, Broue P, Dubuisson C, Cormier-Daire V, Habes D, Chardot C et al (2001) Orthotopic liver transplantation for mitochondrial respiratory chain disorders: a study of 5 children. Transplantation 71(5):633–637

Ducluzeau PH, Lachaux A, Bouvier R, Duborjal H, Stepien G, Bozon D et al (2002) Progressive reversion of clinical and molecular phenotype in a child with liver mitochondrial DNA depletion. J Hepatol 36(5):698–703

Durand P, Debray D, Mandel R, Baujard C, Branchereau S, Gauthier F et al (2001) Acute liver failure in infancy: a 14-year experience of a pediatric liver transplantation center. J Pediatr 139(6): 871–876

Freckmann ML, Thorburn DR, Kirby DM, Kamath KR, Hammond J, Dennett X et al (1997) Mitochondrial electron transport chain defect presenting as hypoglycemia. J Pediatr 130(3):431–436

Freisinger P, Futterer N, Lankes E, Gempel K, Berger TM, Spalinger J et al (2006) Hepatocerebral mitochondrial DNA depletion syndrome caused by deoxyguanosine kinase (DGUOK) mutations. Arch Neurol 63(8):1129–1134

Gillis LASR (2003) Gastrointestinal manifestations of mitochondrial disease. Gastroenterol Clin North Am 32(3):789–817

Goncalves I, Hermans D, Chretien D, Rustin P, Munnich A, Saudubray JM et al (1995) Mitochondrial respiratory chain defect: a new etiology for neonatal cholestasis and early liver insufficiency. J Hepatol 23(3):290–294

Hakonen AHDG, Salemi R, Bindoff LA, Van Goethem G, DiMauro S, Thorburn DR, Suomalainen A (2007) Abundance of the POLG disease mutations in Europe, Australia, New Zealand, and the USA explained by single ancient European founders. Eur J Hum Genet 15:779–783

Kaji S, Murayama K, Nagata I, Nagasaka H, Takayanagi M, Ohtake A et al (2009) Fluctuating liver functions in siblings with MPV17

mutations and possible improvement associated with dietary and pharmaceutical treatments targeting respiratory chain complex II. Mol Genet Metab 97(4):292–296

Kamath BM, Olthoff KM (2010) Liver transplantation in children: update 2010. Pediatr Clin North Am 57(2):401–414, table of contents

Kayihan N, Nennesmo I, Ericzon BG, Nemeth A (2000) Fatal deterioration of neurological disease after orthotopic liver transplantation for valproic acid-induced liver damage. Pediatr Transplant 4(3):211–214

Kirby DM, Thorburn DR (2008) Approaches to finding the molecular basis of mitochondrial oxidative phosphorylation disorders. Twin Res Hum Genet 11(4):395–411

Lee WS, Sokol RJ (2007) Liver disease in mitochondrial disorders. Semin Liver Dis 27(3):259–273

Mancuso M, Ferraris S, Pancrudo J, Feigenbaum A, Raiman J, Christodoulou J et al (2005) New DGK gene mutations in the hepatocerebral form of mitochondrial DNA depletion syndrome. Arch Neurol 62(5):745–747

Mandel H, Hartman C, Berkowitz D, Elpeleg ON, Manov I, Iancu TC (2001) The hepatic mitochondrial DNA depletion syndrome: ultrastructural changes in liver biopsies. Hepatology 34 (4 Pt 1):776–784

Munnich A, Rotig A, Chretien D, Saudubray JM, Cormier V, Rustin P (1996) Clinical presentations and laboratory investigations in respiratory chain deficiency. Eur J Pediatr 155(4):262–274

Nguyen KV, Sharief FS, Chan SS, Copeland WC, Naviaux RK (2006) Molecular diagnosis of Alpers syndrome. J Hepatol 45 (1):108–116

Rabinowitz SS, Gelfond D, Chen CK, Gloster ES, Whitington PF, Sacconi S et al (2004) Hepatocerebral mitochondrial DNA depletion syndrome: clinical and morphologic features of a nuclear gene mutation. J Pediatr Gastroenterol Nutr 38 (2):216–220

Rake JP, van Spronsen FJ, Visser G, Ruitenbeek W, Schweizer JJ, Bijleveld CM et al (2000) End-stage liver disease as the only consequence of a mitochondrial respiratory chain deficiency: no contra-indication for liver transplantation. Eur J Pediatr 159 (7):523–526

Salviati L, Sacconi S, Mancuso M, Otaegui D, Camano P, Marina A et al (2002) Mitochondrial DNA depletion and dGK gene mutations. Ann Neurol 52(3):311–317

Scheers I, Bachy V, Stephenne X, Sokal EM (2005) Risk of hepatocellular carcinoma in liver mitochondrial respiratory chain disorders. J Pediatr 146(3):414–417

Slama A, Giurgea I, Debrey D, Bridoux D, de Lonlay P, Levy P et al (2005) Deoxyguanosine kinase mutations and combined deficiencies of the mitochondrial respiratory chain in patients with hepatic involvement. Mol Genet Metab 86(4):462–465

Sokal EM, Sokol R, Cormier V, Lacaille F, McKiernan P, Van Spronsen FJ et al (1999) Liver transplantation in mitochondrial respiratory chain disorders. Eur J Pediatr 158(Suppl 2): S81–S84

Sokol RJTW (1999) Mitochondria and childhood liver diseases. J Pediatr Gastroenterol Nutr 28(1):4–16

Tadiboyina VT, Rupar A, Atkison P, Feigenbaum A, Kronick J, Wang J et al (2005) Novel mutation in DGUOK in hepatocerebral mitochondrial DNA depletion syndrome associated with cystathioninuria. Am J Med Genet A 135(3):289–291

Thomson M, McKiernan P, Buckels J, Mayer D, Kelly D (1998) Generalised mitochondrial cytopathy is an absolute contraindication to orthotopic liver transplant in childhood. J Pediatr Gastroenterol Nutr 26(4):478–481

Tzoulis C, Engelsen BA, Telstad W, Aasly J, Zeviani M, Winterthun S et al (2006) The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. Brain 129(Pt 7):1685–1692