Methylmalonic and Propionic acidurias: Quick reference guide

Introduction

Methylmalonic acidurias (MMA) and Propionic aciduria (PA) comprise a group of inborn errors of metabolism affecting the catabolic pathway of a number of compounds including the amino acids Isoleucine, Valine, Methionine, Threonine, odd chain fatty acids and cholesterol. Isolated Methylmalonic aciduria is caused by the deficient activity of methylmalonyl-CoA mutase (MCM), a vitamin B12 dependent mitochondrial enzyme whereas PA is caused by the deficient activity of the enzyme propionyl CoA carboxylase, a mitochondrial biotin-dependant enzyme.

The treatment of MMA and PA is complex and requires regular monitoring and frequent therapeutic and dietary adjustments. It is recommended that the treatment and follow up of these patients be supervised by an experienced multidisciplinary team in a tertiary setting, although many aspects of care, including emergency management, can be delivered at the local or secondary level. Patients require regular follow up in order to monitor their clinical condition, complications, nutritional status and growth and to make any changes to treatment as necessary.

Clinical presentation

C	**In newborns with clinical distress and/or suspicion of sepsis organic acidemias must be considered in the differential diagnosis from the outset (table 1)**

C	**After the neonatal period, the clinical presentation of MMA/PA may mimic other more common conditions. Presenting symptoms include:** **- recurrent vomiting with ketoacidosis, abnormal feeding behavior, failure to thrive** **- acute encephalopathy, hypotonia, seizures, movement disorders/stroke-like events, psychiatric symptoms** **- developmental delay** **- neutropenia** **- cardiomyopathy, prolonged QTc interval** **- chronic renal failure in MMA**

Diagnosis

B	**Determination of organic acids in urine and the acylcarnitine profile in blood are the most commonly used investigations to detect MMA and PA. Determination of amino acid concentrations may help in differential diagnosis and treatment. Total plasma homocysteine allows differentiation between the various types of MMA. Enzymatic studies and/or molecular genetic analyses should be performed in specialized laboratories to confirm diagnosis.**

C	**Defects in different genes can cause isolated methylmalonic aciduria. The clinical phenotype is influenced by the underlying enzymatic defect (mut^0, mut$^-$, cblB, cblA and cblD-variant 2) and genotype (*mut*, *MMAA*, *MMAB, MMADHC*). No genotype-phenotype correlations are found in PA.**

D	**Prenatal testing in both diseases is feasible when the index case has been confirmed biochemically and/or genetically, and the carrier status of the parents has been confirmed by mutation analysis.**

Acute management

D	The presence of any one or more of certain clinical or biochemical signs (Table 1) compared to the individual patient's baseline should trigger further evaluation and potential adjustment of therapy and monitoring in order to prevent complications (Table 2). Any acute illness warrants closer monitoring and follow up.
D	During mild illness and without gastrointestinal symptoms, home enteral emergency feeding management is appropriate. There should be provision of adequate energy to meet increased metabolic demands and prevent endogenous protein catabolism.
D	Intolerance or refusal of emergency feeds warrants hospitalization for intravenous therapy. Intravenous fluids containing glucose should be infused and insulin may be used to promote anabolism; lipid emulsion should be commenced early to provide additional calories. Following improvement of metabolic and clinical abnormalities, protein should be rapidly reintroduced. Enteral feeding should be started as soon as possible. Parenteral nutrition is indicated, when enteral feeding cannot be established within 24-48h.
D	Extracorporeal detoxification may be required in severely decompensated patients

Long-term management

C	The most common medical treatments besides the diet used in long-term treatment of MMA/PA are L-carnitine, antibiotics to reduce intestinal flora and vitamin B_{12}.
C	Response to vitamin B_{12} should be assessed in every MMA patient. For responders hydroxocobalamin should be used as long-term treatment.
C	Chronic hyperammonaemia indicates metabolic imbalance and requires investigation and treatment of the underlying cause. Sodium benzoate has been used to treat chronic hyperammonaemia in MMA/PA patients.
D	Drugs containing propionate, valproate, pivalic acid, nephrotoxic drugs and chemotherapy agents should be avoided or used with great caution in patients with MMA/PA. Medications known to prolong the QTc-interval (such as prokinetic drugs) should be avoided if possible. Steroids administered by a systemic route should be avoided if possible, or if unavoidable, should be used with caution. Inhaled steroids seem safe.
C	Dietary management of MMA/PA aims at metabolic stability and normal growth. It is based on adequate energy supply combined with avoidance of prolonged fasting and reduced intake of precursor amino acids through a restricted natural protein diet, commonly supplemented with precursor-free synthetic amino acids. The WHO/FAO/ UNU (2007) safe levels of protein intake provide a useful guide for protein prescription (table 3).
D	MMA/PA precursors free amino acid supplements should form part of the total protein intake if natural protein tolerance is below WHO/UNU/FAO (2007) safe levels of protein intake.
C	Tube feeding may be necessary to avoid catabolism/prolonged fasting, achieve nutritional adequacy, administer medications and supplements and maintain metabolic stability.
C	Liver and/or kidney transplantation has been used as an alternative therapy to conventional medical treatment in MMA and PA patients. Transplantation should be considered in patients with frequent metabolic decompensations where the clinical condition is difficult to stabilize. Transplantation only partially corrects the enzymatic defect; renal and neurological complications may still occur afterwards.
C	The management of the long-term renal complications is based on adequate hydration, drug therapy, hemo- or peritoneal dialysis and ultimately kidney transplantation.

Follow up

D	Regular follow up with clinical, biochemical and dietary monitoring is essential to prevent nutritional imbalance and to detect and treat long-term complications (Table 4).
C	Despite intensive medical treatment, MMA and PA are associated with a high frequency of intellectual disability. Intellectual abilities and cognitive development should be assessed early and reliably to allow timely referral for appropriate intervention.
D	Neurological examination with detailed history of developmental milestones should be a routine part of evaluation in every visit to the metabolic clinic. Input from a pediatric neurologist should be considered in case of acute neurological presentation (encephalopathy/coma, seizures), any suspicion of developmental delay, spasticity/dystonia and movement disorder, epilepsy, hearing or visual field defects..
D	Ophthalmologic assessment (fundoscopy, visual acuity and visual field) and a formal examination by an ophthalmologist to exclude optic neuropathy should be a part of routine evaluation at baseline, at any time of concern and yearly after 6 years of age.
C	One of the most severe long-term complications in MMA is chronic kidney disease (CKD). CKD is characterized by progressive functional abnormality leading to chronic renal failure. Regular measurements of glomerular filtration rate and plasma and urinary MMA are recommended as parameters in the follow-up of patients with MMA. With declining kidney function urinary MMA ceases to be a reliable marker and should be replaced by plasma MMA. Plasma creatinine levels may be less reliable in these patients due to the poor muscle mass and the low protein intake.
C	Cardiac complications include cardiomyopathy and prolonged QTc interval which may be life-threatening and may occur in MMA and PA patients with increasing frequency with age. Therefore ECG and heart ultrasound (echocardiography) are recommended every year. If cardiomyopathy or long QTc is present standard cardiac therapy should be undertaken and metabolic treatment and monitoring should be optimized. .
C	Acute, recurrent acute and chronic pancreatitis may develop in MMA and PA, independently from metabolic decompensations and metabolic control. Diagnosis and management of acute or chronic pancreatitis follows the same principles as in any other case of pancreatitis..
C	Pancytopenia (especially neutropenia) is frequent in MMA and PA and may respond to improved metabolic control. Evaluation with a low threshold to treat infections as well as infection control practices should be performed according to institutional guidelines early in neutropenic patients. .

Table 1 – Bedside differential diagnostics of inborn errors of metabolism presenting with acute encephalopathy

Parameter	Condition								
	UCD	MMA / PA	β-Keto-thiolase deficiency	MSUD	β-oxidation defects	HMG CoA lyase deficiency	HIHA	Mitochondrial/ PC deficiency [e]	PDH deficiency
↑ NH_3	++	+	–	–	+/–	+	+	+/–	–
Acidosis	+/–	+	++	–	+/–	+	–	+	+
Ketonuria[a]	–	++/+++	+++	+/++	–	–	–	+/++	–
Hypoglycemia[b]	–	+/–	–	–	+	+	++	+/–	–
↑ Lactic acid[c]	–	+	+	–	+/–	+	–	++	++
↑ AST & ALT	(+)	+/–	–	–	++	+/–	–	+/–	–
↑ CPK	–	–	–	–	++	–	–	+/–	–
↑ Uric acid	–	+	+	+	+	+	–	+/–	+/–
↓ WBC/RBC/Plt	–	+	–	–	–	–	–	+/–	–
Weight loss	–	+[d]	+	+/–	–	–	–	+	–

Non-standard abbreviations include: MSUD, maple syrup urine disease; HMG-CoA lyase, 3-hydroxy-3-methlyglutaryl-CoA lyase; HIHA, Hyperinsulinism-hyperammonemia syndrome; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase.

[a]Ketonuria (++ - +++) suggests OA in neonates

[b]Hypoglycemia and hyperammonemia ("pseudo-Reye") are predominant in 3-HMG-CoA-lyase deficiency (more than in PC deficiency)

[c]Lactic acid elevation refers to a plasma lactate > 6 mmol/l; lower levels of 2-6 mM may be due to violent crying or extensive muscle activity.

[d] only in neonates

[e] Only type B associated with hyperammonemia but not types A and C

Table 2- Triggers, clinical signs & symptoms and biochemical signs of acute decompensation in organic acidurias

Triggers	clinical signs and symptoms	biochemical signs
Infection	poor feeding	metabolic acidosis (pH <7.3, anion
Fever	vomiting	gap >20 mmol/l, low pCO2 or base
		excess greater than -5 mmol/l)
Prolonged fasting	lethargy	elevated blood lactate (>3mmol/l)
Medication (e.g. chemotherapy,	hypotonia	hyperammonemia
high dose glucocorticoids)		
Prolonged or intense physical	irritability	ketonuria (greater than trace in
exercise, surgery and/or general		infants or greater than + in
anesthesia		children)
Acute trauma, significant	respiratory distress	uric acid and/or elevated urinary
hemorrhage		urea (urea/creatinine>20) as signs
		of catabolism
Psychological stress	hypothermia	neutropenia
excessive protein intake	dehydration and weight loss	thrombocytopenia

Table 3 - FAO/WHO/UNU 2007 safe levels of protein and energy intake for different age groups

Energy requirements					Protein requirements*	
Age	**kJ/kg/day** FAO/WHO/UNU 2007		**kcal/kg/day** converted from FAO/WHO/UNU 2007		**Age**	**g/kg/day**
Infants (y)	Males	Females	Males	Females	Infants (y)	
0.5	335	340	80.0	81.2	0.1	1.77
					0.2	1.5
					0.25	1.36
					0.5-1	1.31
Children (y)					Children (y)	
2.5	348	334	83.1	79.8	1-10	0.84-0.90
5.0	315	305	75.2	72.8		
10	275	248	65.7	59.2		
15	230	193	54.9	46.1	11-16	0.92-1.14
Adults (y) (moderate activity, 70 kg)					Adults (y)	
18-29	183	159	43.7	38.0	>16	0.84-0.87
30-59	175	148	41.8	35.3		
Adults (y) (moderate activity, 50kg)						
18-29	212	180	50.6	43.0		
30-59	212	183	50.6	43.7		

* The FAO/WHO/UNU (2007) have set safe levels of protein intake titrated as an age adjusted mean + 2 SD. Values for safe levels of protein intake apply to males and females

Table 4 – Metabolic follow-up, monitoring of diet and nutritional status, and long term complications

Assessment	Frequency
1. Metabolic follow-up	
NH_3, blood gases, lactate	Each clinic visit
Quantitative plasma amino acids (3-4h fasting)	Every 3-6 months
MMA plasma and urine	Every 3-6 months
Free carnitine plasma (or dried blood spots)	Every 6-12 months
2. Monitoring of diet and nutritional status	
Diet history	Each clinic visit
Growth (weight, length/height, BMI)	Each clinic visit
Clinical examination e.g. skin, hair	Each clinic visit
Albumin, pre-albumin	Every 6 months
Bone health (calcium, phosphorus, alkaline phosphatase, magnesium, parathyroid hormone, 25-OH vitamin D)	Annually, more frequently in case of chronic kidney disease
FBC, zinc, selenium, ferritin, folic acid, vitamin B_{12}	Annually
3. Monitoring of long term complications	
Neurological examination with detailed history of developmental milestones	Each clinic visit
Kidney function (glomerular and tubular function)* (serum creatinine, urea, electrolytes, cystatin C, uric acid, urinary electrolytes and protein loss, GFR)	Biochemistry, urine: every 6 mo* GFR*: annually, beginning at 6y or earlier, if other renal function markers are abnormal
Pancreas (amylase &lipase)	Every 6 months
Heart (ECG, echocardiography)	Baseline → annually, start at 6 y
Formal developmental / IQ assessment	At defined ages
Ophthalmologic assessment	Annually after 6 y
EEG, MRI, formal hearing test	If clinical suspicion / indication
Dentist / oral care	Regularly

* Monitoring of kidney function should be performed every 6 months in MMA; in PA annual monitoring is sufficient and GFR measurement is only indicated if other renal function markers are abnormal

Grade of recommendation: D

Legend

Grades of recommendations

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}.
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}.
D	Evidence level 3 and 4; or Extrapolated evidence from studies rated as 2^{+}.

Good practice points

GCP	Recommended best practice based on the clinical experience of the guideline development group.

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