MedNut Mail

The How, When, Where, Which and Why of pharmacotnutrition

MELAS and pharmaconutrition

Y Coleman

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https://medicationsandnutrition.online

Commentary

MELAS (Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like) is caused by mutations in mitochondrial DNA and is considered to be an Inborn Error of Metabolism. Clinical manifestation is typically before the age of 40 therefore presentation in older adults is very unusual.

I found this man (details in Case Study) several years ago and there was very limited available research – comprising mostly of case-studies with n = 1, and mostly on children; now case studies for adults are being published more commonly.

If there is limited research - and the rarer the clinical issue the more likely there will be very limited available evidence, regardless of quality of the evidence - then our determinations must be guided by first principles which are necessary to underpin the clinical management decisions; the case studies guide treatment direction -

- will doing nothing cause harm? – yes, as the harm caused by the disorder would continue to progress relatively rapidly; effective treatment may stabilise the condition and/or slow progression;
- will the proposed interventions cause more harm than benefit? – unlikely, based on case study findings;
- will the proposed interventions confer benefit? – most likely based on case study evidence.

MELAS falls under the dysfunctional mitochondria umbrella and raises both nutrition and pharmacological issues – and a combination of both. This person was prescribed a number of drugs with seriously compromising nutritional consequences such as -

- inhibition and uncoupling of oxidative phosphorylation – typically related to aspirin, and includes other drugs,
- CoQ10 depletion with consequent negative impact on energy production at the mitochondrial level – typically related to statins,
- inhibition of biotin and carnitine transport and uptake – includes drugs such as verapamil and sodium valproate.

We don’t know the degree of negative impact on the body’s nutritional requirements as a consequence of -

- the diagnosis of MELAS,
- the prescribed medications to manage the diagnosis,
- whether the relevant transporters are negatively impacted chemically (inhibition, substrates) or

mechanically (fewer in number, deformed structures),
- the adequacy of the provided diet to meet the (presumably increased) metabolic nutritional requirements.

Prolonged seizures may lead to neuronal injury and a distorted Blood-Brain-Barrier which can make seizure control in MELAS patients extremely difficult. Several of the antiepileptic drugs such as valproic acid, carbamazepine, phenytoin, and phenobarbital have a high potential for mitochondrial toxicity. Metformin is contraindicated in patients with mitochondrial disorders, especially MELAS and diabetes, due to its associated increased risk of lactic acidosis.

Some nutrition interventions that have been found to confer benefits for some individuals with MELAS include –

- agents related to modulating Electron Transfer Chain - vitamin B1, B2, B3, folic acid and CoQ10;
- Nitric Oxide precursors - Levoarginine;
- energy buffers - creatine;
- agents related to metabolism - Biotin, B12, Levocarnitine;
- agents related to mitochondrial biogenesis - vitamin B3;
- Vitamin K - phylloquinone, menadione. Very important in sphingomyelin synthesis;
- Ascorbate – significant neuronal anti-oxidant;
- succinate - dysregulation of succinate synthesis, and therefore ATP synthesis, happens in some genetic mitochondrial diseases;
- dichloroacetate - inhibits pyruvate dehydrogenase kinase resulting in the inhibition of glycolysis and a decrease in lactate production;
- arginine and citrulline. Citrulline is converted to arginine in the kidneys and is an important source of arginine for the body's non-liver functions (watermelon is an excellent source of citrulline).

It would be a concern if clinicians focussed on other aspects of Care and did not consider the underlying pharmaconutrition issues with their metabolic consequences as exampled by the prescription of atorvastatin to this person.

What interventions will you initiate when you see someone with a diagnosis relating to dysfunctional mitochondria – will you -

- request carnitine status be clarified?
- ensure vitamin D, B12, and folate levels are within acceptable ranges?
- recommend a thiamine intervention (administered at a different time from drugs that inhibit or a substrate for the thiamine transporters)?
- recommend regular monitoring of glycaemic status?
- consider a complete multivitamin and mineral intervention, possibly administered a couple of times per day?

Conclusion

The nutritional consequences of the pharmacological interventions in this person diagnosed with MELAS are an excellent example of application of case study research and application of clinical first principles in relation to pharmaconutrition.

Case study

Medical History with Nutritional Aspect

Amputation	☐	Constipation	☐	Dysphagia	☐	MND	☐
Anaemia	☐	CVA	☐	Enteral Feed	☐	MS	☐
Arthritis	☐	CVD	☐	Falls	☐	Osteoporosis	☐
Cancer	☐	Dementia	☑	Fracture	☐	PD	☐
CCF	☐	Dentures	☐	Frailty	☐	Pressure Area	☐
Chest Infection	☐	Depression	☐	Gout	☐	Renal	☐
COAD	☐	DM Type 1	☐	Hypertension	☑	Ulcer	☐
Confusion	☐	DM Type 2	☐	Incontinent	☐	UTI	☐

Food Allergies: Pork and bacon

Other: MELAS, asthma, blindness

Biochemistry with Pharmaconutritional Consequences

Na:	143	mmol/l	Hb:	129	g/L	Albumin:	40	g/L	BSL:		mmol/l
K:	3.6	mmol/l	Lymph:	1.87		Total Protein:	69	g/L	HbA1C:	6.2	
Urea:	3.8	mmol/l	MCV:	89	mmol/l	B12:	339	pmol/L	INR:		
Creatinine:	0.068	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:	0.78	mIU/L

Other: eGFR > 90, Ca 2.27, CRP < 3, Mg 0.82, phos 0.93, T4 14.2

Medications That May Adversely Affect Nutritional Status

Drug	Vits + Mins	bpp	>90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drlg	d m	Dys	BSL
Allopurinol			☐	NV	D			☑				☐	☐	☐
Aspirin	C, Fe		☑	NV				☐				☐	☐	☑
Atorvastatin			☑	NV	CD	↑	↓	☑				☐	☐	☐
COLOXYL WITH S			☐		D			☐				☐	☐	☐
Levetiracetam	D		☐	NV	D	↑	↑	☐				☑	☐	☐
MOVICOL			☐	N	D			☐				☐	☐	☐
PANADOL OSTEO			☐	NV	CD			☐				☐	☐	☐
PHYSIOTENS			☐	N	CD		↓	☐				☑	☐	☑
Verapamil	carnitine		☑	N	CD			☐				☑	☐	☐

Extra drug: Irbesartan HCT

Comments – medication and nutrition impacts (direct and indirect) only

Relatively recent biochemistry does not indicate any pharmaconutrition interactions. However advisable to monitor plasma proteins on a regular basis as 3 prescribed medications are transported by albumin and change in albumin status will alter their therapeutic effects and expression of their side effects.

Regular aspirin intake is a contributor to iron deficiency in the very elderly.

Caffeine increases aspirin absorption.

Aspirin reversibly decreases gastric vitamin C levels; Vitamin C (960 mg/day) attenuates aspirin-induced gastric injury. Advisable to administer vitamin C in maximum doses of 500 g to optimise benefit as this seems to be the maximum load for transporters.

Chronic use of coloxyl + senna may promote excessive loss of water and electrolytes, especially potassium, and their regular monitoring recommended.

Recommendation that vitamin D status be monitored on a regular basis and intervention initiated as appropriate whilst levetiracetam prescribed.

Verapamil inhibits carnitine, choline ad thiamine transport and uptake.

Dietary levels of caffeine intake in conjunction with paracetamol inhibit antinocieception.

Concurrent ingestion of paracetamol and iron resulted in increased rate of iron absorption and decreased extent of drug absorption; the authors advise drug and iron to be administered at different times from each other.

Physiotens negatively impacts thiamine and choline availability via the transporter system.

Statins such as atorvastatin interfere early in the cholesterol metabolic pathway and consequently decrease production of -

- vitamin D - vitamin D intervention recommended,
- CoQ10 - important in cellular energy production; CoQ10 intervention recommended.

Therefore advisable to monitor cholesterol status on a regular basis and ensure intervention is still required.

Aspirin, atorvastatin and physiotens are all associated with alteration to glycaemic status therefore advisable to monitor glycaemia on a regular basis.

Past history of (recent) phenytoin and sodium valproate prescription both of which are associated with negatively impacting B12, folate, vitamin D, biotin and carnitine levels therefore advisable to

- check B12 and folate status, and

- Mr ABB may benefit from a short term (90-120 days) low dose biotin (max dose 300 mcg/day) and carnitine intervention.

Mr ABB is a tall, slender, charming gentleman who was sitting in his room when I went to speak to him. During our discussion we ascertained he is lactose intolerant therefore advisable to ensure the excipients (ingredients) of all prescribed medications do not include lactose.

Riboflavin is important in energy production at the mitochondrial level; Mr ABB may benefit from a short term (90-120 days), low-dose (11-13 mg/day) riboflavin intervention - this won't cause harm and may confer benefit.

Mr ABB is a “young” older man with a shortened life expectancy; both atorvastatin and physiotens include loss of appetite in their side effect profiles. Given the current problems with attaining an adequate food intake, and further the anticipated shortened life expectancy, advisable to review necessity for continued prescription of atorvastatin.

Mr ABB has an unusual and complex medical diagnosis that necessitates the application of first principles and highlights the importance of pharmaconutrition considerations in his medical management.

What else would you include?

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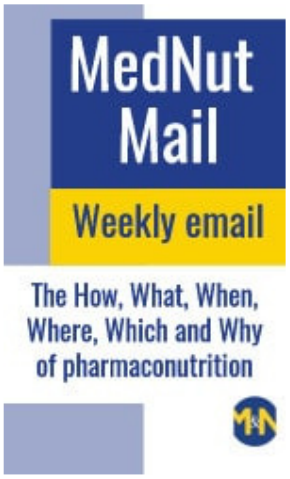

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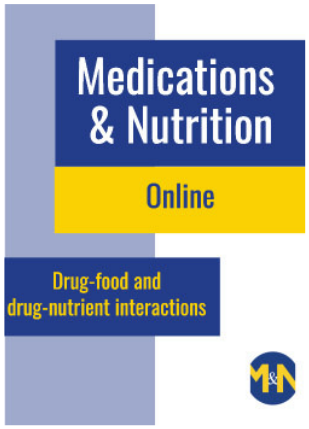

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