Solving the metabolic mysteries of Kryptopyrroluria

Practically unknown in the UK, Kryptopyrroluria can be a hidden cause of nutrient deficiencies and an unsuspected complicating factor in conditions such as Lyme disease and heavy metal toxicity. In part two of her intro to KPU, **GILIAN CROWTHER**, Director of Research at the Academy of Nutritional Medicine, looks at testing and therapeutic approaches.

Following on from part one in *IHCAN's* February edition, which discussed the mechanisms of Kryptopyrroluria (KPU), now we're going to look at what you can do about this "mysterious" condition.

As I outlined last month, KPU is a metabolic disorder that revolves around a glitch in the production and breakdown of haem, the iron-containing part of haemoglobin.

Pyrroles are the "scaffolding" holding together porphyrins, and porphyrins form the ring-like structure that holds iron in the centre of haem.

"Krypto" means "hidden" in Greek: the pyrroles are hidden because they cannot easily be detected, and "uria" means excreted in the urine.

This byproduct of haemoglobin synthesis - 2,4 dimethyl-3-ethylpyrrole - commonly binds to B6 and then to zinc, building an insoluble complex that is flushed out instead of being properly utilised. As Dr Dietrich Klinghardt, MD, PhD, once put it, sufferers are "peeing out an improperly synthesised haem molecule".

Testing for KPU and related nutrient deficiencies

Testing for KPU is done with a urine sample in a tube containing a stabiliser (ascorbic acid in a specific ratio). Ideally before doing the test the client will discontinue taking any supplements that contain the nutrients most frequently lost in KPU for at least five days: vitamin B6, zinc and manganese, as supplemental intake may mask the condition. The sample will ideally be taken in as dark an environment as possible, capped very quickly and stored in the fridge until collected, as kryptopyrroles are very sensitive to light, oxygen and heat. They should reach the laboratory as swiftly as possible without being batched, and be analysed on receipt, as pyrroles swiftly dissipate. Most of the laboratories used in Europe are in Germany, due to their having long recognised this condition, unlike the UK and other countries.

Units of measurement vary: the Kiweno Laboratory that the Academy of Nutritional Medicine AONM uses has a cutoff of 150ng/ml, which is well recognised worldwide, with above that considered elevated.

Low in nutrients?

The next question is whether the patient is low in all of the metabolites mentioned last month. Testing for levels of these needs the caveat that it is hard to identify genuine intracellular and intramitochondrial levels of nutrients at the best of times - especially B6.

As recently as 2016, Whittaker wrote in the *Archives of Biochemistry and Biophysics:* "Transport systems for intracellular trafficking of PLP [the active form of B6] are largely undefined .... poorly understood." [1]. A recent study by Moore et al in *Metallomics* concludes, "Zinc deficiency is currently diagnosed using blood, urine, and hair tests. However, the tests are infamously insensitive, meaning they miss a lot of deficiencies even where symptoms are present", and asserts "there is still a need for a robust biomarker of Zn status".[2]

Manganese, vital for superoxidase dismutase within our cellular powerhouses, mnSOD[3], can only be measured within the mitochondria via electron paramagnetic resonance, atomic absorption, or inductively coupled plasma mass spectrometry, none of which are yet commercially available. We are left with urinary analyses of zinc and manganese that can raise suspicion if the levels are high, and organic acid test markers that give indications of B6 levels.

The Kennedy Krieger Institute Fatty Acid Analysis at Johns Hopkins does often detect low Omega 6 levels[4], unlike other tests of fatty acids that can tend to be calibrated more around an Omega 3 index.

Part one concluded with the section "Is copper a huge missing piece in the puzzle?", suggesting a possible root cause that lies beyond the usual suspects. Testing for bioavailable copper within the cells and mitochondria is fraught with its own difficulties. The usual test for copper is in serum, but a high serum level doesn't automatically mean that copper levels are excessive; instead it suggests it may

Lots of food sources of course, too – but difficult to reach supraphysiological doses with foods

Box 2: Food sources of B6, zinc and manganese

Some good sources of B6:

Chicken	Hazelnuts	Potatoes
Tuna	Pinto beans	Sardines
Walnuts	Halibut	Brussel sprouts
Salmon	Avocados	Cod
Lentils	Chestnuts	Sweet potatoes
Lima beans	Kale	Cauliflower
Blackeyed peas	Whole grain rye	Red cabbage
Brown rice	Spinach	Leeks

Some rich food sources of zinc:

Oysters	Lima beans	Shrimp
Ginger roots	Almonds	Turnips
Pecans	Walnuts	Black pepper
Split peas	Clams	Paprika
Whole grain wheat	Tuna	Chili powder
Whole grain rye	Haddock	Thyme
Whole grain oats	Green peas	Cinnamon

Some food sources of manganese:

Wheat germ	Brussel sprouts	Grapefruit
Green leafy vegetables	Blueberries	Apricots
Spinach	Oranges	Kelp

https://aonm.org/kryptopyrroluria-the-elephant-in-the-room/; https://nutritionsource.hsph.harvard.edu/vitamin-b6/; https://www.researchgate.net/figure/Examples-of-foods-rich-in-zinc-data-obtained-from-NIH2021_fig1_363278687

be unmetabolised, and that there are low intracellular and intramitochondrial levels.

Ceruloplasmin and retinol

Ceruloplasmin is our copper transport protein, carrying more than 95% of total copper in healthy human plasma[5].

Endothelial cells in the liver have been found to each have around 570,000 ceruloplasmin (Cp) receptors[6], and each Cp molecule can bind to 6 to 8 copper atoms[7]. This alone indicates how very important copper is for our organism: its specific significance in KPU was described last month.

The vast number of Cp receptors our cells have also suggests how useful caeruloplasmin is as a marker for copper status, and when measured is indeed often low.

Studies have demonstrated that retinoic acid can stimulate the production of ceruloplasmin[8]. Retinol (true vitamin A - not beta carotene, which is the precursor, and conversion via BCO1 and other genes is often deficient) converts into retinoic acid[9]. The logic is therefore that sufficient intracellular/intramitochondrial copper status, being dependent upon caeruloplasmin status, requires retinol. This can be measured in red blood cells (though expensive).

Therapeutic approaches

The usual therapeutic approach recommended for KPU is to substitute the most obvious deficiencies, ie the nutrients being lost unmetabolised in the urine. We will look first at this traditional approach, and then consider the possible "missing piece of the puzzle".

Increasing food sources of B6, zinc and manganese is a first port of call, but it is hard to achieve supraphysiological doses with foods. It is still a good approach of course to include these in the diet as much as possible (see for example https://aonm.org/kryptopyrroluria-the-elephant-in-the-room/ for a list).

• Safe removal of potential heavy metal toxicity

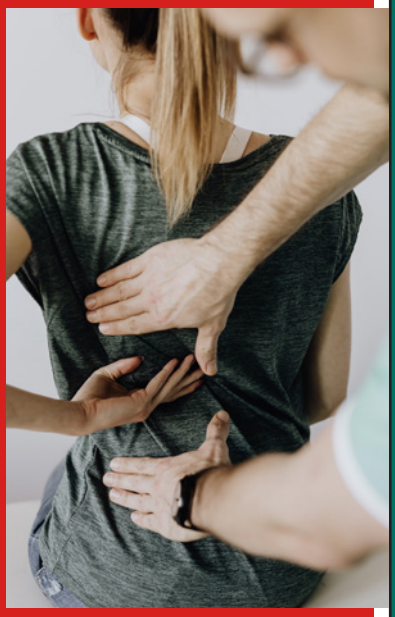
More than 300 enzymes in the body are zinc-dependent, and when zinc cannot be used, other bivalent metals will be substituted, such as lead, cadmium, aluminium or mercury[10]. When you start resubstituting zinc in high enough levels for it to hopefully begin reinserting itself in the enzymes, these bivalent metals will need to be excreted[11].

The Perrin Technique™ is a manual technique developed in 1989 by British osteopath and neuroscientist Dr Raymond Perrin, DO, PhD, and is based on Dr Perrin's theory that different stress factors - whether physical or emotional or from allergies and infections - lead to an overstrain of the sympathetic nervous system.

Further investigation has led to a probable cause of this nervous system overload being a build-up of toxins in the fluid around the brain and the spinal cord. Some of the poisons caused by infection or inflammation in the head or spine flow through channels from the brain into the lymph ducts of the head face and neck. The toxins are also meant to drain down the spinal cord and out into the lymph ducts lying along the spine.

In an ME/CFS sufferer, there is a backflow of these normal drainage points which leads to further toxicity and dysfunction of the central nervous system.

• https://theperrintechnique.com.



• Activate lymph

Preparing an effective detoxification strategy means ensuring that the lymphatic pathways are open. Depending on the patient's status, this could mean rhythmic cranial compression to activate the glymphatic system and allow toxin drainage from the brain, and dilation of the anterior neck veins and other pathways to open the lymphatics. Both the Klinghardt and Perrin Techniques[12] have extensive information on this, and creams to encourage circulation.

• Binders

To buffer the detoxification reactions, the intake of sufficient binders is important.

It is advisable to start these several days before starting to detox the bivalent metals. Chlorella has well evidenced ability to bind[13] and safely eliminate cadmium, lead, mercury and aluminium. Zeolite (Clinoptilolite) - powdered only - has a great affinity for a wide range of heavy metals[14]. Modified Citrus Pectin is also evidenced to provide support in heavy metal chelation[15]. The dosages depend on a number of factors and are best decided between therapist and patient. Rotation is also advisable.

It's critical to take the binder well away from food and supplements (otherwise you risk it binding the trace minerals in those, too). Soluble and insoluble fibre in the diet are also vital.

• Protect kidneys

The kidneys need protection too, due to the huge and unnatural load of pyrroles that are being excreted through them into the urine. Wild garlic *(Allium ursinum)* is known for its nephroprotective effects[16], as well as parsley[17] and horsetail[18, 19].

Sage in the form of *Salvia sclarea* and *Salvia officinalis* has protective mechanisms against cadmium[20]. Melatonin can also help prevent cadmium-induced toxicity[21], but this is an intervention curbed by regulations in the UK, so only relevant for countries where its use is more generally permitted. Other initiatives such as Calcium EDTA that also have substantiation[22] would require guidance by a therapist experienced in their use. Coriander/Cilantro is gentle but effective particularly for mercury, and a silica-rich mix of Inula, Burdock, Horsetail and Wild Celery together with Coriander can be very helpful for detox of aluminium.

Epsom Salt baths provide highly hydrophilic silica via the transdermal route, assisting in the formation of another crucial aspect of detoxification.

Exclusion zone (EZ) water, detailed in the work of Prof Gerald Pollack – "Water Isn't What You Think It Is: The Fourth Phase of Water[23] - and glutathione as our key intracellular antioxidant or its precursors (glycine, cysteine) will provide further cellular support in the detoxification process.

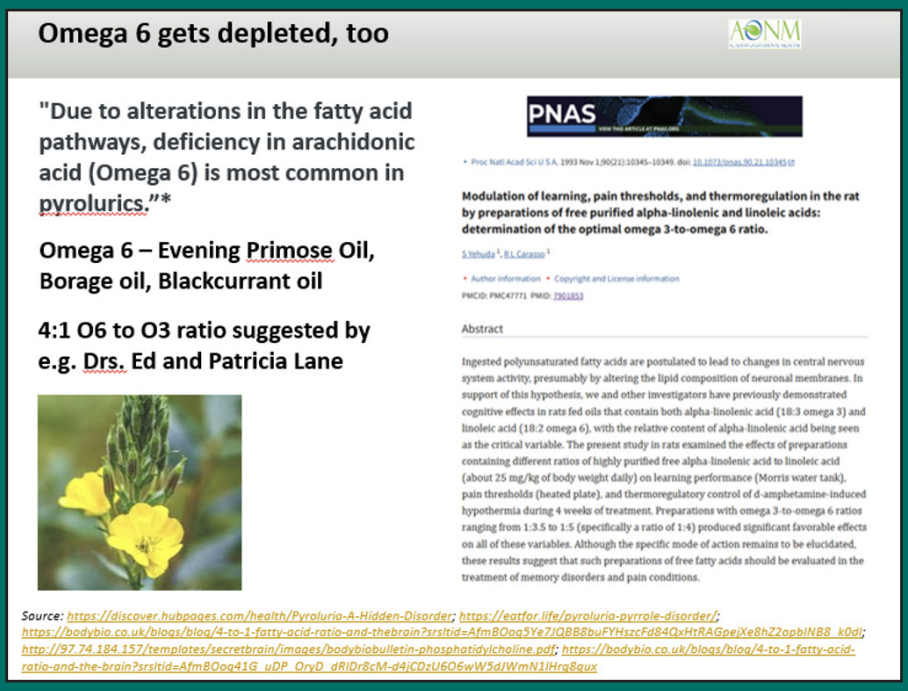
Caution is needed with glutamine, the third GSH precursor, as it can act as an excitotoxin, when the neurotransmitters of KPU sufferers are already on high alert. Better to cautiously provide glutamine-rich foods such as animal protein, seafood, dairy, eggs, nuts, legumes and beans, if tolerated. A good mix of electrolytes will be very supportive, too.

Substitution of the deficient nutrients

The "traditional" approach is to use supplements that provide supraphysiological doses of the nutrients being leached out by KPU. Various combination formulas contain B6, zinc and a matrix of other nutrients to support their absorption. Very sensitive individuals may do better with the nutrients given separately - sometimes in very low doses to begin with (symptoms similar to MCAS - Mast Cell Activation Syndrome - are not unusual in KPU sufferers).

Biochemical Individuality decides whether B6 in the form of pyridoxine or P5P is most bioavailable, so a 50/50 mix of the two is often best. Caution is required if the patient is also suffering from active Lyme Disease, as Borrelia spirochetes, its causative agent, need manganese for their survival[24], so including manganese in the formulation is inadvisable, at least in the first few months of the KPU protocol. Some of these formulations recognise the possible secondary deficiencies of chromium, magnesium and niacin - something to consider in the overall context of your patient's condition.

While replacing zinc, whether individually or in a combination formula, Quercetin can act as a zinc ionophore, meaning it has the ability to transport ions across cell membranes[25]. This has a dual function in an era of continually reactivating SARS-CoV-2, as zinc can also decrease the replication of RNA viruses[26]. Sources of omega-6 should also not be forgotten: nuts, seeds, olive oil, ghee, eggs, as well as evening primrose, borage and blackcurrant oil.



Timescale

How long to continue the therapy? Hopefully symptoms will begin to subside: the therapist will ideally check in with the patient regularly, perhaps using forms of kinesiology (such as Autonomic Response Testing®), and repeating the urine test if wished. Some sources suggest that supraphysiological dosing of the nutrients in question may be necessary for life.

Next level supplementation

Is there another way beyond mere substitution?

There is another approach that perhaps goes further to the root of the defect that has led to the dysregulated pyrroles in the first place, obviating the need for lifelong substitution.

Part one described the logic for providing bioavailable copper needed by ferrochelatase, the copper-dependent enzyme in the mitochondria that could well be the source of the dysfunction.

Apart from being essential for haem synthesis, bioavailable copper is also vital for erythrocyte production and energy generation in the mitochondria, as well as much else[27].

There is therefore huge logic behind using it as a strategy for countering KPU. The question is whether to slot it on as a "Phase 2" after a period of using the traditional approach just outlined, or whether to prioritise this approach to strengthening the mitochondria and (as a consequence, if not directly) repairing likely defects in the haem production pathway.

As outlined in part one, since three of the haem synthesis enzymes are inside the mitochondria, including the first and the last, it makes sense to prioritise mitochondrial support. "You correct kryptopyrroles by correcting the process of making new blood cells with bioavailable copper", as Morley Robbins says in *CU-re Your Fatigue*[28].

Choosing the potentially deeper "root cause" route is unfortunately not simply a matter of providing high-quality copper bisglycinate. Our copper transport protein is caeruloplasmin[29]. "It is ceruloplasmin that makes copper available to our cells, tissues, and organs"[30], and its function is sadly suppressed by a myriad of factors. One huge factor is iron trapping, disrupting the body's iron-ceruloplasmin-copper balance, something that has featured particularly prominently in COVID and post-COVID syndromes[31].

It is not easy to work out whether this is the case if you test with a straightforward iron panel, as iron trapped in tissue (or the mitochondria) cannot be measured in commercial tests, but various markers can provide an approximation. Retinol (genuine vitamin A, not the precursor beta carotene) is the backbone of caeruloplasmin[32], and therefore a key stepping stone in the pathway, but is often deficient in diets too - especially since it can only be obtained from meat and dairy products (a severe issue for vegans).

A conundrum in attempting to resolve KPU the "traditional way" is that a high intake of zinc displaces copper, and also stimulates the synthesis of metallothionein[33]: metallothionein binds up copper much more tightly than it does zinc, making it inactive[34]. The solution in this case would be to give preference to foods containing zinc, whether pumpkin or sunflower seeds, grass-fed beef liver etc., rather than taking high supplemental zinc long term.

The Root Cause Protocol (https://therootcauseprotocol.com) and the book *CU-re Your Fatigue* have a lot more information on navigating the path to making copper available to our cells, tissues and organs.

Studies have not yet been conducted specifically into whether that will always be the answer to the multiple issues that can arise from KPU, but the mitochondria are at the root of health, and supporting them with this vital nutrient in a patient-centred context can only be beneficial.

Ultimately the practitioner needs to make decisions on sequencing KPU therapy based on the evidence from science as well as case studies and clinical observation. Please see https://aonm.org/kpu-webinars.

• Morley Robbins, Founder of the Root Cause Protocol, will be visiting the UK on May 22 to speak on the importance of copper, together with Prof Douglas Kell from Liverpool University, also a great copper expert: see https://bnfm.org.uk.

The bioflavonoid Quercetin acts as an ionophore

"In addition to all of these impressive supportive functions and applications, quercetin's most impressive quality may be its established zinc ionophore activity. As mentioned, an ionophore is a compound that can transport ions like zinc across cell membranes. As zinc regulates immune cell function, this may be able to decrease the replication of RNA viruses."*

Sophora Japonica: high in quercetin

Source: * https://www.avivahealth.com/blogs/articles/ionophores; https://www.kiscience.com/product/broccoli-synergy-powders/

About the author

GILIAN CROWTHER, MA (Oxon), FBANT, mANP, mNNA, CNHC reg., is a fully qualified Nutritional Therapist and Naturopath specialising in complex multisystem disorders. Her key focus is on infectious pathologies and mitochondrial dysfunction.

She studied complementary therapy in Germany for many years before completing her training in the UK. She has been a senior member of the Academy of Nutritional Medicine (www.aonm.org) since 2010, and is their Director of Research. She is a committee member of the General Naturopathic Council (GNC) as well as the British Society for Ecological Medicine (BSEM).

Gilian has featured in IHCAN mag before, spoken at an IHCAN Summit, and was runner-up for the "Outstanding Contribution to the Community" Award in 2018.