

ION™ Profile in Patient Suffering Symptoms of Cognitive Dysfunction Consistent with CFS

An ION™ Profile Includes A Total of 126 Analytes - So When Presented With An ION™ Profile Where Only A Select Few Markers Are Abnormal; Such Markers Take on More Significance

A 47 year old male presented to his clinician with symptoms of cognitive dysfunction and depression. It was considered that primary insomnia was the cause of his mental health concerns including anxiety and agitation. As maybe anticipated, the patient also reports considerable fatigue, apathy and lethargy. The clinician reports a high DAS score. Past history revealed the patient had functional gastrointestinal symptoms that had resulted in an assessment by another Clinician of his gastrointestinal microbiota using a Gastrointestinal Function Profile. Although the treatment of his gastrointestinal microbiota significantly improved his GI symptoms his insomnia, cognition and mental health issues persisted, prompting him to seek further professional assistance. An **ION™ Profile** was ordered to provide the clinician with a comprehensive insight into his patients individual nutritional biochemical function.

Medication & Supplements

The patient is taking 22.5mg of mirtazapine daily for his insomnia as well as finasteride (Propecia) and a 2% topical application of minoxidil (Regaine) for male pattern baldness. Mirtazapine and finasteride are the likely cause of the raised glucarate on the patient's **Organix™ Profile** shown below. Both are known to undergo extensive hepatic metabolism, with finasteride the greater of the two. Urinary glucarate excretion is an indicator of overall hepatic detoxification demand. Thus, administration of medications such as finasteride, which result in stimulation of hepatic P450 activity tend to produce increased excretion of glucarate.

32 Glucarate 11.0 H  <= 10.7

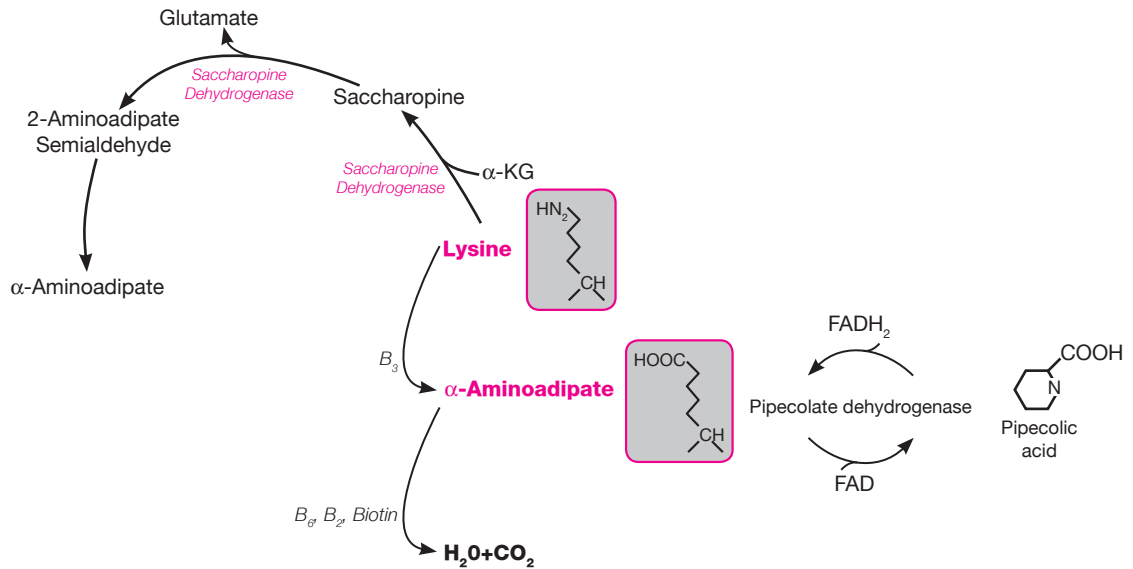
Amino Acids

The only noted abnormality on the 20 plasma amino acid profile is a finding of high lysine as shown below.

Limiting Amino Acids



Lysine Metabolism



The major pathway for lysine degradation occurs in the mitochondria and involves transamination of the ϵ -amino group to alpha-ketoglutaric acid (α -KG) through the intermediate, saccharopine as shown above. The metabolism of lysine onto α -amino adipate is dependant on the presence of α -KG as cofactor for the enzyme saccharopine dehydrogenase. Indeed, studies have found that availability of α -KG is the limiting factor in the catabolism of lysine.¹ It is therefore interesting to note that the patient has undetectable levels of α -KG on the accompanying **Organix™ Profile** as shown below.



B-Vitamins & Lysine Metabolism

Referring again to the diagram above, one can see that if α -KG is in short supply, inadequate amounts of b-vitamins, namely, B_3 , B_6 , B_2 and biotin may limit its metabolism down the alternative pathway to pipecolic acid formation. With the extensive array of analytes provided by the **ION™ Profile**, we are able to examine adequacy of B_6 , B_2 and biotin. Interestingly the markers relating specifically to these vitamins are shown to be high as seen below.



There are no studies to support the notion that b-vitamins may limit the metabolism of lysine to pipecolic acid, however, given the information on this **ION™ Profile** combined with the current knowledge of lysine metabolism, it is a reasonable suggestion to supplement the patient's diet with these b-vitamins. Raised levels of odd-chain fatty acids are another biochemical marker that has been linked to biotin deficiency.² Results of the patient's erythrocyte fatty acid profile below show high levels of some odd-chain fatty acids, further supporting the notion that the patient may benefit from supplementation with b-vitamins including biotin.



Pipecolic Acid

An increase in pipecolic acid formation is the normal consequence of high lysine levels due to limited availability of α -KG. This alternate pathway for lysine metabolism usually functions as an overflow pathway and takes place in peroxisomes.³ Pipecolic acid has been shown to modulate neuronal activity by binding to GABA receptors in the brain in a number of animal studies⁴ and it is thought it has the same action in humans. Stimulation of GABA receptors by pipecolic acid could be partly responsible for the patient's symptoms of insomnia, agitation and anxiety. Supplemental α -KG and b-vitamins may help reduce lysine levels and in turn pipecolic acid levels.

Perspective: ION™ Profile in Patient Suffering Symptoms of Cognitive Dysfunction Consistent with CFS

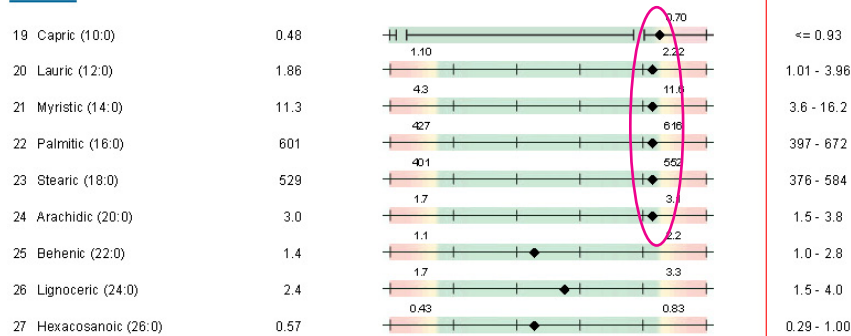
Hypertriglyceridemia & Alpha-Ketoglutarate

The other important question to pose is why α -KG levels are low. Formation of α -KG is predominantly under the control of the enzyme glutamate dehydrogenase (GDH), which catalyses the reaction leading to production of α -KG and ammonia from glutamate. GDH is primarily regulated by the energy balance in mitochondria. When ATP levels are low, GDH is activated to provide more α -KG to drive the Krebs' Cycle. Palmitic acid, the principle fatty acid in plasma is a key inhibitor of GDH.

Palmitic Acid

Palmitic acid is the first fatty acid produced during lipogenesis (i.e. fatty acid synthesis). Raised palmitic acid is one of the common signs of the metabolic syndrome, whereby elevated insulin levels occur in conjunction with raised serum triglycerides and cholesterol. In patients' with metabolic syndrome, there is stimulation of fatty acid synthesis, leading to an increase in palmitic, stearic and arachidic acids. Plasma fatty acids profiles are typically used to assess individual levels of fatty acids in hypertriglyceridemia, however, the referring clinician has a preference for ordering erythrocyte fatty acid profiles as part of the **ION™ Profile**. Below are the results for erythrocyte saturated fats including palmitic, stearic and arachidic in erythrocytes. While it is hard to draw any direct correlation between erythrocyte saturated fatty acid levels and plasma saturated fatty acid levels, one might assume from the pattern of high-normal levels of saturated fatty acids in erythrocytes below that levels in plasma may be just as high or even higher.

Saturated



Markers of Hyperinsulinemia on the Organix™ Profile

A particular combination of metabolic markers from this patient's **Organix™ Profile** suggest that the patient may have a degree of hyperinsulinemia. Below are the analytes, pyruvate, β -hydroxybutyrate, and the branch-chain keto acids, α -ketoisocaproate, α -ketoisovalerate and α -keto- β -methylvalerate. Pyruvate is the end-product of glycolysis, whereas β -hydroxybutyrate is a common ketone body. Lastly, the branch-chain keto acids serve as markers of muscle tissue catabolism. Undetectable levels of each of these analytes could be interpreted as a sign of hyperinsulinemia. Insulin is the body's storage hormone for fuel; so while insulin levels are raised, glycolysis, ketosis and muscle tissue catabolism will all be suppressed.

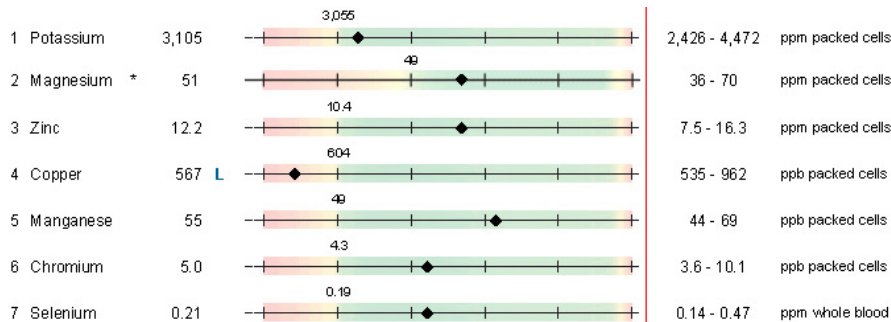


Symptoms of Hyperinsulinemia/Hypoglycemia

From a clinical standpoint, patients' with hyperinsulinemia often complain of symptoms of weakness, poor memory, poor concentration, irritability, apathy, fatigue and anxiety. Each such symptom was recorded as occurring frequently and with severe effect for this patient. Some specific symptoms related to hypoglycemia resulting from hyperinsulinemia include slurred speech, confusion, and feelings of weakness. Likewise, the patient reported these symptoms to occur frequently and with severe effect. At the time of writing it was not clear whether the patient had undertaken any glucose tolerance tests, which included measurement of insulin levels. Given the pattern of markers on the patient's **ION™ Profile** and the corresponding symptoms, it would be prudent for the referring clinician to have the patient undertake a fasting insulin test.

Nutrient Elements

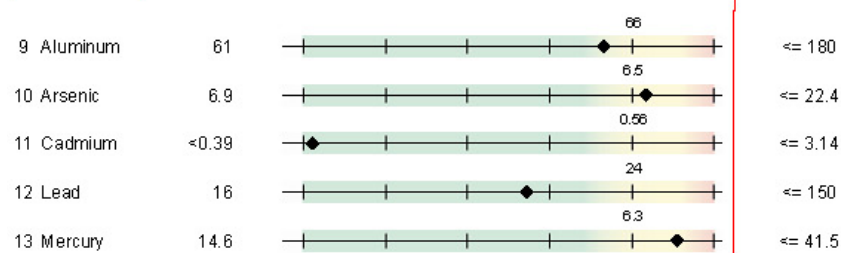
Another key feature of the patient's **ION™ Profile** was low erythrocyte copper. The patient is reported to be taking 4-5 grams of vitamin C per day, which is known to reduce the absorption of copper. There is also an extensive body of evidence linking copper deficiency with cardiovascular disease, elevated cholesterol and impaired glucose tolerance. These associations reinforce the possible hyperinsulinemia associated with the pattern of markers on the **Organix™ Profile**.



Copper Deficiency Exacerbates Mercury Toxicity

Copper deficiency leads to an up-regulation in the synthesis of metallothionein (MT). Among other things, MT has a very high affinity for mercury, which in the context of the high erythrocyte mercury level shown below, emphasizes the importance of correcting the copper deficiency in this patient. A high level of mercury could also be crucial in the clinical context for this patient. Poor cognitive dysfunction, anxiety, depression and insomnia can also be attributed to mercury toxicity. Further urinary provocation testing may be warranted.

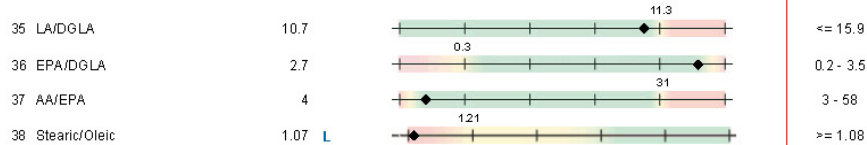
Toxic Elements



Stearic/Oleic Ratio & Cancer Risk

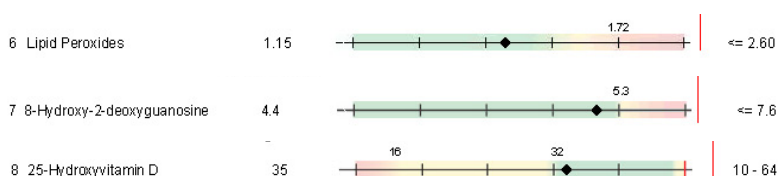
The final significant abnormality to note on this patient's **ION™ Profile** is a very low stearic/oleic acid ratio or the saturation index (SI) as it is commonly referred to. Stearic acid is the most common saturated fatty acid, while oleic acid is the most common monounsaturated fatty acid. A reduction in SI has been observed in patients with breast and other cancers. Furthermore, some studies have found a high SI to be protective against breast cancer.

Ratios



Other Oxidative/Toxic Stress Markers

8-hydroxy-2-deoxyguanosine and lipid peroxides are two markers which provide a good general indication of oxidative or toxic stress. Likewise, vitamin D is a marker that has been correlated with cancer risk. However, all of these are within normal limits as seen below, which casts doubt on the likelihood that the low SI value is a reflection of early malignant tissue growth. After taking into account effects due to dietary intake of olive oil, which



contains oleic acid, the referring clinician should consider appropriate further testing if they deem there is any significant risk for malignant tissue growth.

Summary

As highlighted at the outset, the fact that this patient has relatively few abnormal markers, out of such a diverse array, affords the clinician the opportunity to 'zero-in' on the abnormal markers and target therapy accordingly. In such cases, the clinician should carefully consider each marker and its possible role in the aetiology of the patient's symptoms/condition.

Many of the abnormal amino acid, fatty acid and **Organix™ Profile** markers could be interpreted as hyperinsulinemia; leading to poor utilization of normal fuel sources such as carbohydrate, fat and protein. Hyperinsulinemia would explain many of the patient's neurological symptoms, however, most hyperinsulinemia patients present as being overweight rather than underweight so this casts doubt on such a diagnosis. The patient may respond well to simple supplementation with α -KG to drive the Krebs's Cycle and hence improve the patient's energy. Further tests to determine the presence/absence of insulin dysfunction should be considered.

Marginal deficiencies of particular b-vitamins may also be important in the context of raised plasma lysine levels. Supplementation with these nutrients should be considered.

The simple finding of low copper and high mercury could also be significant in the context of this patient's symptoms. Appropriate steps should be taken to decrease the patient's toxin metal load, while increasing their detoxification capacity.

We welcome further input and feedback regarding this case via our comment portal.

References

1. Kamoun P, et al. Plasma lysine concentration and availability of 2-ketoglutarate in liver mitochondria. *J Inherit Metab Dis.* 2002;25:1-6.
2. Mock DM, et al. Effects of biotin deficiency on serum fatty acid composition: evidence for abnormalities in humans. *Journal of Nutrition.* 1988.;118(3):342-8.
3. Cox RP, Dancis J (1995) Errors of lysine metabolism. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 7th edn, vol 1. New York: McGraw-Hill, 1233-1238.
4. Takagi T, et al. Central pipecolic acid increases food intake under ad libitum feeding conditions in the neonatal chick. *Neuroscience Letters.* 2003;347(2):93-6.