

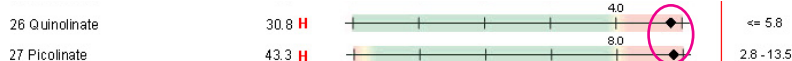
ION™ Profile in Patient with Chronic Lymphocytic Leukemia (CLL)

Very High Quinolate & Picolinate Signal Strong Activation of The Kynurenine Pathway; Secondary to Cell-Mediated Immune Activation. Over-Stimulation of The Kynurenine Pathway Can Diminish Tryptophan Levels To The Point That T-Cell Responses Are Inhibited; Leading to Poor Prognosis in Leukemia Patients

A 63 year old female with CLL was recommended to undertake an **ION™ Profile** by her referring doctor as part of a work-up for a comprehensive nutritional treatment program. Other relevant pathology included: raised liver enzymes; high anion gap; low platelet white cells, neutrophils and lymphocyte counts; all consistent with active CLL. Symptom wise, the main complaints consisted of: fatigue; poor concentration, memory and comprehension; joint pain; weakness; leg cramps; dry skin; poor night vision; itchy eyes and swollen eye lids; blurred vision; bloated & belching; shortness of breath and frequent urination.

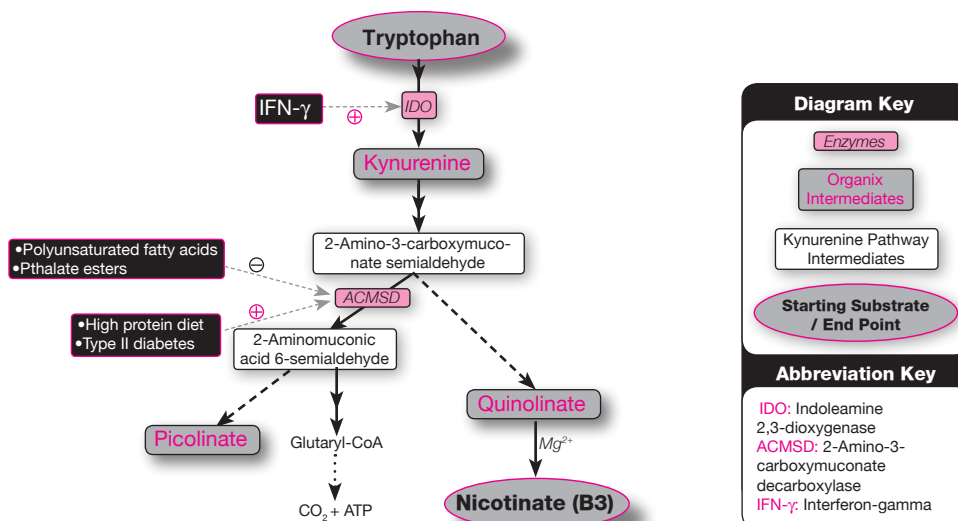
Quinolate & Picolinate

Quinolate and picolinate are the two highest markers on the patient's **ION™ Profile**. Quinolate is over 5 times the upper 95% reference interval whereas picolinate is over 3 times the upper 95% reference interval.



Kynurenine Pathway

In order to understand the significance of raised quinolate and picolinate levels, it is useful to consider the abbreviated diagram of the kynurenine pathway below.



IDO Is The Key

The preceding diagram shows IDO as the key inducer of tryptophan degradation in the kynurenine pathway. Indeed, IDO is the 'rate-limiting' enzyme for the kynurenine pathway and is expressed in a variety of tissues.¹ It is highly induced by bacterial and viral infection, which is mediated mainly by IFN- γ .²⁻⁴ This results in increased tryptophan degradation along the kynurenine pathway. The tryptophan degradation induced by IDO during infection plays a role in the defense mechanism against the infectious pathogens. It results in tryptophan depletion that in turn suppresses the growth of many types of viruses, parasites and infectious bacteria.¹

Systemic IDO Induction Causes Dangerous Systemic Tryptophan Depletion

In most cases of infection, the induction of IDO is limited to the tissues infected with the pathogens.¹ For example, during a pulmonary infection with an influenza virus, the IDO induction is limited to the lung.⁵ This localized effect suppresses the growth of the pathogens through IDO-mediated tryptophan deprivation in the infected area. However, in the case of malignant tissue growth or leukaemia, there is often a systemic induction of IDO, whereby the resulting tryptophan deprivation can affect all tissues.¹ This can lead to a decrease in the synthesis of serotonin, with resulting symptoms of depression^{6, 7}, anxiety⁸ and IBS^{8, 9}, all of which have been linked to activation of IDO.



From the very high levels of quinolinate and picolinate, we might expect systemic levels of tryptophan to be diminished in this patient. The **ION™ Profile** includes the **20 Plasma - Amino Acid Analysis** so we are able to see the extent to which induction of IDO is affecting plasma levels of tryptophan. Above we can see that tryptophan is the only essential amino acid below the 95% reference interval, indicating significant depletion. The patient reports mild depression, anxiety and diarrhea, which indicates she may be in the early stages of tryptophan depletion. If strong induction of IDO is allowed to continue, we might expect these symptoms to worsen. Many other essential amino acids are low, which suggests the patient's protein intake and absorption is compromised. Muscle tissue catabolism secondary to leukemia may also be a factor as low threonine levels have been linked to heightened catabolism.

Escape of Tumor Cells From Immune Surveillance By IDO Expression

Immune escape is a crucial property of cancer progression. Researchers have established that most human malignant tumor cells express IDO.¹⁰ Animal models of cancer have demonstrated that tumours expressing a high level of IDO effectively escape the immune surveillance of the host by degrading local tryptophan, which in turn inhibits T-cell responses.¹⁰ As such, the extent of IDO expression in tumor cells can be used as a prognostic tool.¹ The very high levels of quinolinate and picolinate on this patient's result are cause for concern and suggest the leukemia may not be responding to treatment as well as hoped.

Neurotoxic Quinolinate

Some of the intermediate metabolites of the kynurenine pathway are neuroactive. Of these, much attention has been focused on quinolinate. When injected intracerebrally, quinolinate has been shown to cause neural death.^{11, 12} This toxicity is due to the activation of the sub population of neural glutamate receptors sensitive to N-methyl-D-aspartate (NMDA).¹³ Quinolinate has been shown to accumulate within the brain in a broad spectrum of patients with inflammatory neurological diseases.¹ Due to its effect on NMDA receptors, patients with high quinolinate will often complain of insomnia, as is the case for this patient.

Quinolate & Oxidative Stress

Given that induction of IDO is an inflammatory response of the cell-mediated immune system, elevation of kynurenine pathway intermediates is often accompanied by oxidative stress. Indeed, some of the intermediates of the kynurenine pathway, such as xanthurenate and quinolate, have been shown to be strong pro-oxidants. Studies have linked high levels of these intermediates with high levels of the DNA oxidative damage marker, 8-hydroxy-2'-deoxyguanosine.¹⁴ The pro-oxidant effects of induction of the kynurenine pathway are also evident in this patient with the raised 8-hydroxy-2'-deoxyguanosine. This suggests it would be prudent for the clinician to use antioxidant therapy in conjunction with anti-inflammatory agents to stem induction of IDO.



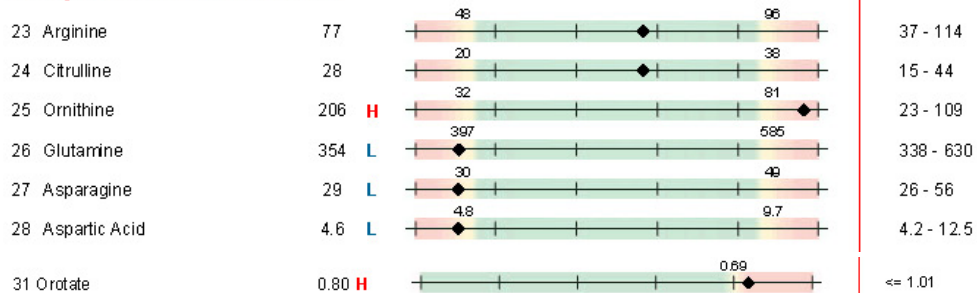
Botanical Treatment of IDO

In light of the newly discovered role IDO plays in the regulation of the body's inflammatory response, a number of studies have explored the efficacy of certain noted anti-inflammatory botanical extracts or actives. Active components of turmeric,^{15, 16} green tea,¹⁷ garlic,¹⁸ st john's wort,¹⁹ rosemary,²⁰ cinnamon,²¹ chocolate²² and even beer²³ have been shown to inhibit the expression of IDO in different capacities. Turmeric is one of the botanicals with a number of studies demonstrating its efficacy in stemming IDO expression. Such a botanical could be considered as a possible adjunctive treatment for this patient.

Ammonia Overload & Asparaginase

Markers from the **20 Plasma - Amino Acid Analysis** and **Organix™ Profile** suggest the patient has a derangement in their ammonia metabolism and detoxification. High levels of ornithine combined with high orotate indicate the patient's ability to detoxify ammonia via the urea cycle is impaired.

Urea Cycle and Ammonia Detoxification



Use of the drug, asparaginase might explain some of these findings. Asparaginase is an enzyme that catalyses the hydrolysis of asparagine to aspartic acid and ammonia. Asparaginase is often given as a chemotherapeutic agent to patients with leukemia.²⁴ It takes advantage of the fact that all leukemic cells are unable to synthesize the nonessential amino acid asparagine, and therefore have to depend on circulating asparagine for supply. Asparaginase, however, catalyses the conversion of L-asparagine to aspartic acid and ammonia. This deprives the leukemic cell of circulating asparagine. It is not known whether the patient had used or is using asparaginase as a chemotherapeutic agent.

Calcium D-Glucarate and Urinary Glucarate

The very high urinary glucarate exhibited by this patient is normally a sign of liver induction due to prescription drugs/medication, which undergo extensive first-pass hepatic metabolism.²⁵ However, the patient did not list any medications on her accompanying *Personal Health Assessment* form when submitting the specimen. The patient was, however, taking calcium D-glucarate which is known to elevate urinary calcium D-glucarate levels.²⁶



Potassium & Magnesium

Another abnormality on this patient's **ION™ Profile** are low levels of potassium and magnesium. Low potassium levels have been documented in numerous studies of leukaemia patients including patients with CLL.²⁷ It is thought this may be due to kidney dysfunction, which is a common feature in leukemia patients.²⁸ The referring clinician may want to prescribe potassium supplements to offset the deficiency. The patient reports to be taking magnesium, however, her levels are still suboptimal. The referring clinician might suggest the patient increase her daily dose.



Perspective: ION™ Profile in Patient with Chronic Lymphocytic Leukemia

Functional CoQ10 Deficiency

Elevation of succinate and hydroxymethylglutarate are specific indicators of a functional CoQ10 deficiency. A statin drug by the name of Lovastatin is commonly used to treat acute myeloid leukaemia,²⁹ however, it is not known whether such medication has been previously used by this patient. Excluding this, the deficiency may simply be due to oxidative stress secondary to the CLL.



Functional Carnitine Deficiency

The last significant abnormality to highlight is a functional deficiency of carnitine as revealed by a very high level of adipate. Studies in children and adolescents with leukaemia have shown levels of carnitine to be depressed in the early stages of disease.³⁰ Thus, supplementation with carnitine may be warranted.



Summary

High levels of quinolinate and picolinate on this patient's test signify that there is strong induction of IDO by IFN- γ . Quinolinate levels in cancer and leukemia patients can serve as a useful prognostic tool, with high quinolinate levels correlated with poor treatment prognosis.¹ Pharmaceutical, nutritional or botanical adjunctive treatments aimed at suppressing IDO activity should be a major consideration for the patient. Ongoing monitoring of the kynurenine pathway via follow up **Organix™ Profile** testing will be important to monitor treatment efficacy.

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