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A Brief Historic Overview of Clinical Disorders Associated with Tryptophan: The Relevance to Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM).

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Abstract: Last century there was a short burst of interest in the tryptophan related disorders of pellagra and related abnormalities that are usually presented in infancy.^{1,2} Nutritional physiologists recognized that a severe human dietary deficiency of either tryptophan or the B group vitamins could result in central nervous system (CNS) sequelae such as ataxia, cognitive dysfunction and dysphoria, accompanied by skin hyperpigmentation.^{3,4} The current paper will focus on the emerging role of tryptophan in chronic fatigue syndrome (CFS) and fibromyalgia (FM).

Keywords: tryptophan, pellagra, gamma interferon, chronic fatigue syndrome, fibromyalgia, vitamin B12

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Tryptophan Metabolism

Until the year 2000, research into the specific attributes of the serotonin pathway and its role in neuro-psychiatric disorders was double that of other aspects of tryptophan metabolism.⁵ Experimental tryptophan depletion tests were devised to ascertain the influence of serotonin metabolism on cognition, mood and behavior.⁵⁻⁷ Brief tryptophan depletion tests in normal human subjects, for example, provided consistent evidence for its role in impaired memory consolidation and reduced visual perception.^{7,8} Older studies of prolonged dietary depletion of both tryptophan and niacin were known to lead to severe pellagra, with neurological and extensive inflammatory mucosal membrane changes. These occurred within one to two months of a depleted diet.⁹ In recent decades, however, the involvement of this essential amino acid in the kynurenine pathway has been elucidated.^{5,10} This has in part explained some of the pathological processes of pellagra.

Protein catabolism had long been recognized as the big picture metabolic response to all noxious bodily stimuli such as trauma, infection and neoplastic processes. Upon further analysis of the separate amino-acid constituents of proteins, the degradation of tryptophan emerged as a major contributor to the catabolic process,^{7,10-14} amongst its other critical functions such as neuromodulation. The intimate relationship in the kynurenine pathway between tryptophan, gamma-interferon and 2-3-dioxygenase (IDO) as an immuno-modulatory mechanism has since been substantiated.^{10,15} The kynurenine pathway is also linked to the synthesis of nicotinamide adenine dinucleotide (NAD) from quinolinic acid, and it is up-regulated by neurodegenerative and other inflammatory triggers.¹⁰ This discovery of the existence of two tryptophan metabolic pathways in the CNS and peripheral nervous system has challenged researchers to discriminate between the consequences activation of these dual paths.¹⁰⁻¹⁴

There have been subsequent advances in technologies, such as developments in magnetic resonance imaging (MRI) and positron emission tomography (PET),¹⁶ as well as an increased range of available biochemical and genetic tests.¹⁰ These newer techniques have generated data from specialist molecular biologists at cellular and micrometabolic levels. This sophisticated phase of research has increased our understanding of the physiological mechanisms that underpin basic

principles and observations in medicine. The information is extremely complex, and there tends to be a time lag before it is incorporated into clinical application.

Some Clinical Disorders

The gastrointestinal tract is the nutrient gateway to the body and little is known about tryptophan activity in this area. The combination of malnutrition, malabsorption and metabolic inefficiencies is difficult to unravel. Resultant physical defects from tryptophan depletion can range from mild to severe and can be hard to detect and interpret.^{17,18}

Tryptophan absorption¹⁹⁻²² and metabolic utilization²³ are vulnerable to both primary inborn genetic errors and secondary gut disturbances. In addition, there are several inherited autoimmune diseases of the bowel that affect absorption, such as celiac and Crohns disease.^{5,17,18} These conditions usually do not become apparent until adulthood. Case reports of intestinal autoantibodies to tryptophan hydroxylase have occurred in adults, associated with bowel dysfunction and other systemic autoimmune disorders.²⁴⁻²⁷ At the present time, these various conditions are not completely understood.

Rose¹ (1972) outlined the clinical issues of that era. He also detailed three inborn errors including Hartnup Disease, hypertryptophanemia and 3-hydroxy-kynureninuria. Sabator and Ricos²⁸ reported the presence of kynurenine irregularities in 5% of 830 institutionalized children with mental retardation. Other primary abnormalities of childhood²⁹⁻³³ including tryptophanol glycine absorption disorder²³ have subsequently been documented.

Hartnup Disease is an autosomal recessive condition that is no longer included in neonatal screening programs.^{34,35} This disease is thought to have the same community prevalence as phenylketonuria. It is noted for its clinical variability and onset can occur in adulthood. The physical phenomena resembling pellagra³⁶ in Hartnups Disease responds to treatment with either nicotinamide or neomycin. Carcinoid tumours,² drug side effects,³⁷ and nutritional inadequacies can also present with secondary pellagrous states.⁴

The Relevance of Tryptophan to CFS/FM

The potential connection between the kynurenine pathway and CFS was initially made in 1991³⁸ and with FM in 1993.³⁹ This hypothesis was recently revived as more evidence of tryptophan pathway



dysfunction in CFS/FM has since accrued.^{40,41} CFS/FM could involve serum tryptophan level deficiency,^{42,43} and impaired immune-modulatory function has been demonstrated at the gamma-interferon, IDO stage of metabolism.^{38,44} In addition, there appears to be some resemblance between CFS/FM irregularities and those found in other medical conditions.^{45,46}

Clinical Outline

CFS/FM constitutes a definite single syndrome. There is a consistent, recurring pattern of core symptoms in affected populations.⁴⁷⁻⁴⁹ Some physicians prefer the hybrid classification of overlap syndrome, whereas a few patient support groups opt for the term myalgic encephalomyelitis (ME). The differences lie in theoretical explanatory constructs. Uncertain fluctuations in the course and outcomes of individual patients confound some aspects of scientific analysis.

The signs and symptoms of the condition are well documented in the specialist CFS/FM literature.⁴⁷⁻⁴⁹ Patients present with extreme exhaustion, which is aggravated by exertion and altered sleep patterns. Concentration and memory is impoverished^{45,50,51} and patients experience visual disturbances^{48,49} and unfathomable pain.^{5,48,49} They may suffer inexplicable gastrointestinal and urogenital tract discomforts.^{27,52,53} Amongst less obvious symptoms are ataxia, myopathy, lowered thyroid and cortisol levels, food intolerances and puzzling skin conditions.⁴⁷⁻⁴⁹

Tryptophan Status in CFS/FM

In 1975, Moldofsky and colleagues⁵⁴ looked to serotonin in an attempt to explain the “non-restorative sleep syndrome” of fibrositis (later termed fibromyalgia). In a 1978 study, patients’ tryptophan levels were noted to be lowered.⁴² This observation was repeated by Yunus and colleagues⁵⁵ in 1992. The extensive studies of Russell and colleagues³⁹ were undervalued at that time. Russell and colleagues discovered an abnormality in the conversion stage of 3-hydroxy kynurenine in the CNS in FM patients.^{39,48} Since then, research into the attributes of tryptophan in the context of CFS/FM has continued.^{42,43,56,57} A couple of subsequent studies examined amino acid urinary profiles and other biochemical parameters in CFS patients and controls, without specific mention of tryptophan.^{58,59}

There are several possible explanations for the observed decrease in tryptophan levels in CFS/FM patients. This decrease may be due to any primary genetic disorder, or may be due to malabsorptions created by an idiopathic irritable bowel syndrome,^{52,53} food intolerances, bacterial overgrowth and other bowel disorders.^{16,17} Silent or chronic infections can increase metabolic demands for tryptophan and vitamin B12. Nicotinamide absorption can be reduced through severe diarrhea. These listed observations imply that tryptophan, nicotinamide and B12 deficiencies can become a complication of CFS/FM.^{40,42,60-63} Evidence for the requirement of L-carnitine, zinc⁴² and intravenous vitamin solutions⁶⁴ is circumstantial. This question of nutrient substrate deficiency warrants investigation along formal medical protocols rather than the less structured methods of complementary and alternative medicine models. It is also important to establish if there is a point at which the decline in available metabolic fuel reaches a critical level and structural morphological damage becomes irreversible, leading to chronically impaired health.

Gamma-Interferon and Other Immune Dysfunctions

CFS/FM has, in part, been recognized as an immune deficiency syndrome.^{47-49,65} Bell⁴⁷ was at a loss to explain the immunological profile of the CFS/FM patient; however, he appreciated that it was still early days in the field of cytokine research. He divided the observed irregularities into categories, based on either overactivity or underactivity of the immune system. Underactivity was reflected in a decreased number and function of natural killer cells,⁶⁵⁻⁶⁷ a decreased mitogen response and decreased antibody levels, particularly in the IgG subclasses, in response to infections. In contrast, up-regulation or overactivity of the immune system involved elevated levels of gamma-interferon and other cytokines. CD8 lymphocytes might increase in number with a consequent effect on the CD4:CD8 ratio. Multiple allergies (atopy)⁶⁸ and autoantibody production could be activated. He later considered whether the prolonged malaise observed in CFS could be due to the persistence of infection caused by impaired patient immunity.⁶⁵ He suggested that another factor might involve failure of an initial immune defense response by the host, leading the host to shut down and therefore be unable to proceed along the pathway of resolution.



Lloyd and colleagues⁶⁷ had already documented aspects of “disordered immune regulation” in 1989 in their CFS patients. They discovered that this abnormality related to the host response and could not be attributed to any specific viral infectious agent. They were aware that the therapeutic use of interferons in other medical conditions could produce severe CFS-like symptoms as a side effect.⁶⁹ They anticipated that gamma-interferon would be implicated in CFS illness complications.

Kerr and colleagues⁴⁴ performed extensive studies of patients infected with parvovirus 19. They detected the continued presence of the alpha-tumor necrosis factor and gamma-interferon in both the acute and convalescent phases of this infection. They associated these anomalies with the prolongation of a fatigued state. Kerr and his co-workers were amongst those researchers who proposed that “immune control of the virus may not be efficient”.^{67,70–73} This feature might, in addition, explain the presence of under-recognized neuropathic pain of subclinical Zoster sine Herpete⁷⁴ and of any other infectious and avitaminotic states in CFS/FM patients.^{4,5}

Conclusion

Contemporary tryptophan research examines the up-regulation of the kynurenine pathway by neurological and psychiatric disorders and autoimmune, neoplastic and infectious diseases. The ultimate aims of these studies are to further the understanding of the neurological consequences of these illnesses and to improve their treatment prospects.^{7,10–14}

There are comparative clusters of signs and symptoms in both patients with CFS/FM and in those whose conditions relate predominantly to the kynurenine pathway. Thus, CFS/FM patients could benefit from investigations searching for primary errors of tryptophan metabolism and other kynurenine pathway pathologies.^{10,34,60}

In 1986, Mersky⁷⁵ stated that “a lack of adequate technology and a proper unwillingness to undertake hazardous investigations for obscure symptoms may encourage a false attribution of psychological symptoms to physical illness”. He listed examples of some conditions that had been reclassified as organic in nature. He recommended that the diagnostic status of the patient be reviewed if warranted.

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