A Case for Nutritionally Supporting Mitochondrial Function and Associated Metabolic Processes in Patients with Huntington's Disease

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Abstract

Huntington's Disease (HD) is an autosomal dominant disorder in which the major gene expression is in the Central Nervous System (CNS). It is characterised by the appearance of progressive chorea and dementia, usually in adult life, and complicated by variation in symptoms even within the same family. Since the first clinical description of HD, both clinical and neuropathological parameters have become increasingly defined. However, the aetiology and its pathogenesis continue to be elusive and sixteen years after the discovery of the mutant huntingtin (htt) gene the disease continues to present more complexities. This study elucidates that, currently, the energy metabolism model combined with the excitotoxicity hypothesis seem strong candidates for the age-related expression of selective apoptosis and neurodegenerative decline evident in HD. Strong evidence exists which correlates an optimal level of nutrition, targeted at correcting energetic dysfunction, with an extended pre-symptomatic period and ensuing slow disease progression. Supporting mitochondrial function, the liver's detoxification pathways, monitoring inflammatory responses and combating the generation of free radicals (FRs) with adequate antioxidant supply are all core strategies in supporting a person living with the threat of HD. Cachexia and disordered amino acid (AA) metabolism are known contributors to a weakened state and acceleration of clinical symptoms and must be addressed. Rather than wait for the discovery of a possible cure or signs of an irreversible decline in health associated with disease onset, it would seem prudent that HD patients take positive steps towards supporting their brain function. Consideration of metabolic modifiers as indicated by the use of functional testing procedures may provide a complementary and early intervention approach. This may help mediate and forestall further neuronal damage while preserving vital function in a disease which has been described as "genetically programmed cell death in the human CNS".[1]

Introduction

The village of Avoch is a fishing community sheltered by the inner reaches of the Moray Firth coastline in north east Scotland. It has a population of around 1,000 people and represents a focus of HD which has been identified through the early work of McWilliam [2] and Lyon [3]. The coastal regions of Grampian and Highland are historically noted for their fishing and farming industries which have ensured that village communities, and the traditional nuclear family structure, continue to thrive. The prevalence of HD in this remote area is 10 per 100,000 which is considerably higher than the European statistic for the clinical disease of 5.5 per 100,000[12]. The former statistic is probably still an underestimate, as pre-symptomatic cases were excluded from this more recent study [4].

The author has lived within this community for most of her life and has witnessed at first hand the devastating effects of HD on the family life of friends and neighbours. This paper presents a personal opportunity to add to the volume of research into HD, however small, with the ultimate aim of stimulating further interest in the clinical research required to certify nutrition as having a viable role in ameliorating the symptoms and prolonging disease onset in Huntington challenged patients.

HD is a hereditary disease that involves slow, progressive atrophy of the medium, spiny neurons of the caudate nucleus, putamen and globus pallidus as well as the frontal cortex of the brain [5] with an equal likelihood of affecting males and females. It is generally transmitted as an autosomal dominant trait caused by a mutation of the huntingtin (htt) gene located at the short arm of chromosome 4 which causes a trinucleotide CAG expansion [6]. Wild-type htt presents up to 35 glutamine residues, while its mutant form shows 38 or more, and this is now accepted as the diagnostic parameter for HD, although the juvenile variant may exhibit up to 250 CAG repeats [7]. This childhood form of the disease is most often inherited from the paternal line as an increase in the size of the mutation is known to occur more often during spermatogenesis [8,9]. Htt is a highly conserved protein within the body [10] and is widely expressed in neural and non-neural tissues with relatively high expression in neurons, testes, ovaries and lungs [11]. Neurons are damaged when the mutated protein aggregates and interferes with normal brain metabolism and function, leading to affected axonal transport and cell death, but the mechanism remains poorly understood.

At a behavioural level, HD is characterised by irritability, obsessions, compulsions, hallucinations, impaired memory, decreased executive functions and dementia, all of which inexorably progress through the pattern of disease. The cognitive deficit is accompanied by motor alterations which include both involuntary and voluntary movements. Motor restlessness, dystonia and chorea are characteristic involuntary movements, while voluntary movements can be affected by bradykinaesia, lack of coordination and delayed initiation of movements as well as impairment in their modulation [13]. Onset of disease is usually in early to mid- adulthood [14], although juvenile and late onset forms are well documented [15]. On average, patients can suffer 15-20 years of symptomatic illness and although medications may decrease the severity of the chorea or diminish behavioural symptoms, they do not increase patient survival or substantially improve their quality of life [16].

Review of Literature

The American physician, George Huntington, has been credited with first studying Huntington's Chorea (HC) in 1872 [17]. Huntington knew nothing of the disease's pathophysiology and in the intervening years, despite diligent efforts, little has changed. Although the genetic basis of the disease has been decoded, the mechanism of its pathology is still not fully understood. The advent of pre-symptomatic predictive testing has not lead to any decline in the disease as had been hoped [18] and others had predicted [19], and the suffering of affected families continues.

The ability to devise novel therapeutic strategies in HD is linked to the development of animal studies [20,21]. Interestingly, these animals develop symptoms such as motor dysfunction, loss of body weight and muscle mass and the marked neuropathological changes evident in human HD [22,23].

The mechanisms by which neuronal degeneration and cell death are being generated in HD may include excitotoxicity [24,25,26], oxidative stress [27], inflammatory processes [28], protein aggregation [29]and energy deficit [30]. In addition, recent clinical evidence emphasises an active role for the kynurenine pathway in the disease progression [31,32]. An imbalance of the toxic and neuroprotective metabolites of this pathway can cause excitotoxicity and energy disruption within the cell with devastating results. The precise mechanism is still under intense investigation. Excitotoxicity refers to the death of neurons as a result of exposure to excitatory AAs such as glutamate. In HD, it is thought that this process might be the result of a reduced threshold for glutamate toxicity that could occur in neurons with compromised

energy metabolism, causing otherwise normal levels of this excitatory neurotransmitter to become toxic [33,34]. The relevance of impaired energy metabolism to HD pathology is also suggested by the effects of the toxin 3-nitropropionic acid (3-NPA). The enzyme succinate dehydrogenase, which is involved in the Tricarboxylic Acid Cycle (TCA) and the Electron Transport Chain (ETC) during ATP synthesis, is irreversibly inhibited by this mycotoxin in animal studies [35]. Humans who survive accidental 3-NPA toxicity develop choreiform movements and dystonia [36,37]. Others have suggested a link between excitotoxicity and a decreased activity in glutamate transporters resulting in increased extracellular glutamate levels [38]. *In vivo* support exists for oxidative stress as being part of HD pathology [39] and increased FR production in HD patients [40]. Superoxide dismutase up-regulation has also been proved in a HD cell model [41]. From the research it is not yet clear whether mitochondrial dysfunction and the resultant oxidative stress are primary changes in pathology or a consequence of the early neuropathological changes in HD. It has been argued that mitochondrial changes may be secondary events [42]. However, even as a secondary event mithochondrial dysfunction is likely to seriously impact on the devastating pathological process.

The CNS is particularly vulnerable to any variation in energetic resources due to the elevated metabolism of neuronal cells and their constant demand for glucose and oxygen. As a result, any alteration in energy metabolism represents a potential risk for loss of neuronal viability [43]. An early study in mitochondrial bioenergetics analysed mitochondrial function in HD brain tissue and identified a severe decrease in Complex II and III activity in the ETC of HD caudate nucleus [44]. These findings have since been confirmed and expanded to include a defect of Complex IV activity [45] and yet further research found the same defect in caudate and putamen but not in other brain regions examined [46]. Evidence from animal studies reveals an inter-relationship between excitotoxicity and mitochondrial dysfunction in HD which can be supported by a biochemical defect in the enzyme aconitase which converts citrate to iso-citrate in the TCA cycle [40]. PET scans have demonstrated glucose hypometabolism in the brain striatum and cerebral cortex [47,48] where metabolic changes in the brain tissue exhibits increased lactate levels [49]. Others confirmed this finding by administering coenzyme Q10, which is an essential cofactor of the mitochondrial respiratory chain [50] It was shown that a significant decrease in cortical lactate concentration could be achieved which was then reversed on withdrawal of therapy. Coincidentally, this same study found elevated levels of inorganic phosphate in HD muscle which would implicate defective energy metabolism of the muscle fibres – tissue not previously thought to be clinically implicated in HD. Although one study did not confirm these findings [51], subsequent others

have [52,53], one of which was able to demonstrate that a lesser but still significant decrease in ATP synthesis was also present in pre-symptomatic patients [53] This implied that these energy defects in muscle could be used as a possible biomarker in the future for disease onset and progression. Those combined findings provide evidence for a generalised energy defect in HD and a possible link between mutant htt and defective mitochondrial function outwith the CNS. Transgenic mouse models present an *in vivo* means by which to test possible therapies to address flaws in energy metabolism. If, as the evidence suggests, energy impairment plays a critical role in cell death and neurodegeneration an obvious therapeutic strategy will be to use compounds that could improve mitochondrial metabolism in an attempt to compensate for any disease related defects. One potential treatment is the ETC component coenzyme Q10 (CoQ10) or ubiquinone, which is a potent antioxidant that protects against glutamate toxicity *in vitro* [54] and can increase brain concentrations of CoQ10 in mature and older animals. It can also increase brain mitochondrial concentrations and has been demonstrated as being efficacious in experimental models of neurodegenerative diseases [55]. One such study showed that it provides dose-dependant protection against striatal lesions produced by the succinate dehydrogenase inhibitor malonate [56], shows excellent protection against 3-NPA neurotoxicity and also protects against depletions of reduced coenzyme Q9 and reduced CoQ10 induced by the toxin's effect [57]. Another novel approach has been creatine administration to increase phosphocreatine levels and buffer energy depletion. Creatine is known to be produced endogenously from arginine and glycine in the liver and kidneys and is a critical component in maintaining ATP levels and ameliorating the severity of many of the mechanisms associated with HD [58]. Creatine has also been found to protect against increases in lactate concentrations in the striatum produced by 3-NPA *in vivo* and to delay the neuropathological progression of HD [59]. There is an increasing volume of research to suggest that energy impairment plays a critical role in HD pathogenesis. Abnormalities in mitochondrial energy metabolism may precede and contribute to the increased oxidative stress and disturbances in neuronal calcium homeostasis that occurs in the brain and peripheral cells including fibroblasts and lymphocytes [60,61]. Based on this information the concept of the "mitochondrial spiral" has been introduced [62]where both genetic and environmental factors are believed to be implicated [62].

The features of the disease described in this review of literature support the following hypotheses, which help to explain the alterations which occur in body biochemistry and which may be supported by nutrition intervention in patients with HD. They include:

- *Excitotoxicity* as a result of receptor overactivation which leads to inflammatory events and oxidative stress as shown by the research studies of Siesjo [24], Beal *et al.* [63], Choi [25], Saito *et al.* [26], Guidetti *et al.* [31].
- *Mitochondrial dysfunction* leading to *metabolic damage, oxidative stress and secondary excitotoxicity* as elucidated in the research studies of Novelli *et al.* [33], Lees [43], Beal *et al.* [30,56], Shoulson [64], Borlongan *et al.* [35], La Fontaine *et al.* [27] and Ryu *et al.* [58].
- *Aggregation of the htt protein* which is believed to further metabolic insult as the disease progresses (Mangiarini *et al* [20] ; Tabrizi *et al* [40]).

This summarises the physiological and biochemical findings on the mechanics of a brain suffering from HD. They have formed an important basis for a current understanding of the pathogenesis of the disease and are a vital component when therapeutic approaches, such as nutrition, are being considered. Each researched component of the disease process represents specific therapeutic opportunities which are currently being tested in genetic models of HD, transgenic mouse models and human clinical trials. Challenges exist which include the uncertain ability of these preclinical studies to predict therapeutic efficacy in humans, highlighting the need for human clinical trials and focusing on how to perform neuroprotective trials in pre-symptomatic individuals while shielding them from unwanted genetic information.

Research to date has unsurprisingly concentrated on the genetics and intricate biochemistry of this fatal disease in an attempt to find the key that locks away the mystery of a centuries old condition that never affects only one family member. Until that day, there would appear to be a strong case for the promotion of nutrition as a therapeutic factor in maintaining good health, extending the pre-symptomatic phase of the clinical disease and improving the quality of life in symptomatic HD victims. [65]

Discussion

Environmental factors

The possibility that environmental factors may affect HD in humans is supported by two studies showing that monozygotic twins with identical CAG repeat lengths can display different ages of onset, clinical symptoms and behavioural abilities [66,67]. These findings can relate with a Swedish study which cited stochastic epigenetic and pre- and post-natal

environmental factors as being influential in the phenotypic differences of non - HD monozygotic twins[68]. A recent analysis of Venezuelan HD kindreds at Lake Maracaibo also strongly implicates environmental factors as modulators of HD pathogenesis [69]. These kindreds represent the largest and most studied HD population in the world and were instrumental in enabling science to use genetic and clinical data in order to localise the HD gene on chromosome 4p16.3 , discover the defective gene and identify the nature of its mutation. The majority of the Venezuelan individuals live in extreme poverty with poor sanitation and exist on a diet which is marginal. Most are fishermen exposed to potential pollutants from an oil industry that lines the lake shores[70]. The afore mentioned analysis[69] has shown that phenotypic expression, such as age of onset, disease duration and onset of physical and mental symptoms are variable and suggests that modifying factors exist. A statistical model designed for this study confirmed that approximately 40%of the variance not attributed to a specific variable was due to genes other than the HD gene and that the remaining 60% had an environmental basis. However, it is still unclear whether the age of onset of HD is influenced primarily by additional genetic or environmental factors or by a combination of both. It would therefore be advantagious to isolate those factors in a bid to prolonging the unsymptomatic years and postponing the onset of disease.

Nutrition & Genetics

Many details of offending htt protein interactions, cleavage, conformational changes, aggregation and proteasomal breakdown have been clarified in the last decade [71] and various pharmaceuticals have been proposed based on those mechanistic models[72]. Modern imaging techniques have been able to demonstrate a structural disease progression in pre-clinical HD [73] and groundbreaking foetal cell transplantation is emerging as a potential treatment [74]. However, systematic studies are required before any definite conclusions can be drawn as to the efficacy of various approaches and this is unlikely to happen soon owing to the comparatively small number of patients diagnosed with the disease.

As a family disease, HD forces its members to cope with disturbing events and untimely deaths [75]. When a person begins to exhibit signs of disease onset in mid-life, it is easy to understand why depression and suicidal tendencies are high risk factors of HD [76]. Predictive genetic testing became an option as a diagnostic aid in 1993. This has raised complex implications and ethical issues which may include autonomy, confidentiality, surrogate decision making and the withholding and withdrawal of treatment [77]. To date, this test

shows a low uptake [78]. It is a principle of functional medicine that nutrition and environment can have a powerful effect on gene expression – food choices can directly influence gene expression and modify health by affecting cellular function [79]. In the past decade, nutritional research has undergone an important shift in focus from epidemiology and physiology to molecular biology and genetics. It is now recognised that compounds of dietary origin can be potent signals that influence the metabolic programming of cells and have an important therapeutic role in the control of homeostasis [80]. It is evident that as well as their function as fuel and cofactors, micronutrients can have important effects on gene and protein expression and accordingly on metabolism [81]. The molecular structure of a nutrient determines the specific signalling pathways that it activates and this fine-tuned molecular specificity explains why closely related nutrients can have different effects on cellular function [82]. Taking this into account we may postulate that people who are at high risk of inheriting HD would benefit greatly from being made aware of the influence that nutrition might exert on postponing disease onset and ameliorating symptoms. Rather than a HD candidate waiting for signs of an irreversible decline in cognitive and physical abilities to emerge, it would seem prudent to support the body systems and the brain in particular.

Nutritional approaches

It is widely recognised that nutritional deficiencies are prevalent in the general population and are a major public health issue. People carrying the gene for HD will have a specific genetic handicap so every factor that might apply generally, may carry even more significance for them.

In the early stages of the disease, depression resulting from diagnosis can cause a loss in appetite and changes in eating habit. Weight loss is common among HD patients [83]. It is therefore important to identify these nutritional alterations and to find strategies to cover the increased kilocalorie and nutrient requirements. Maintenance of body condition as the disease progresses is one of the most important areas for the nutritionist to consider. Recent studies have shown that early stage patients change to a pro-catabolic phenotype with alterations in various markers of fatty acid breakdown and aliphatic amino acids [84]. In addition, low fasting plasma concentrations of the branch chain amino acids leucine, isoleucine and valine [85] contribute to the marked cachexia common in HD [86]. Taken in combination, the research suggests that AA imbalance and metabolic disturbance are possible indicators of disease onset and that early nutritional intervention, supporting the

body's metabolic pathways, is advocated. In addition, studies have shown that a Huntington patient, with a BMI close to normal, has a slower disease progression [87].

The need for micronutrients

As already discussed, compounds of dietary origin including vitamins and minerals,act as necessary cofactors for the synthesis and function of mitochondrial enzymes and other compounds that support mitochondrial function. Diets deficient in micronutrients can accelerate mitochondrial decay and contribute to neurodegeneration [88]. Deficiencies of nutrients required for any component of the TCA cycle or ETC can lead to increased production of FRs and damage to mitochondrial DNA. Other damaging events include the formation of advanced glycosylation end-products which occur as a consequence of poor blood sugar control [89] which can be a feature of early HD [90]. Evidence indicates that this occurs via the uncoupling of a cell's mitochondrial energy production system causing apoptosis and resultant oxidant release [91]. Combination antioxidant therapy for people with a genetic risk of brain inflammation shows potential [92,93] as does the use of the hydroascorbate form of vitamin C which is able to penetrate the blood brain barrier and protect the brain from oxidative damage [94].

Along with providing antioxidant nutrients and their precursors and compounds known to increase the efficiency of endogenous antioxidant systems, it would seem appropriate to ensure any cofactors required for the enzymes involved in liver detoxification processes are also present in the diet in clinically relevant amounts.

However, while research would seem to support the use of antioxidants, the exact dosage and ratios of antioxidants and cofactors necessary to achieve clinically relevant responses in HD are still largely undefined. From the literature review it can be seen that further complications exist – many of the mitochondrial dysfunction studies have been performed with animals, not humans, and most have investigated only one or two antioxidants and not the full spectrum of antioxidants and minerals known to be involved in healthy mitochondrial bioenergetics. The most frequently researched molecule in this field would appear to be CoQ10 which is a known antioxidant with a high degree of hydrophobicity and universal presence in biological systems. As such, it is capable of buffering the adverse consequences of FRs produced in the inner mitochondrial membrane during ETC activity. Studies into the effects of CoQ10 on the energy metabolism defects in HD over a period of a decade include definitive work conducted by Koroshetz *et al* [95], Matthews *et al* [57], Beal and Shults[55], Shults [96], Andrich *et al* [97], Dhanasekaran and Jun [98]and Young *et al* [99]. The

combined data would suggest that oral CoQ10 may reduce impaired mitochondrial function in HD, decrease cortical lactate and is relatively safe and well tolerated across a wide dosage range. However, more randomised controlled trials are warranted to confirm its safety and nutritional promise as a clinically effective neuroprotectant

Essential Fatty Acids

The relevance of essential fatty acids (EFAs) in HD is another popular area of research. A randomised, placebo-controlled, double-blind study has shown that highly unsaturated fatty acids are beneficial in HD and has linked the use of unsaturated fatty acids with preventing protein aggregation and activating the ubiquitin-proteasome system [100]. However, caution should be applied when interpreting this particular paper as one of the authors has a potential conflict of interest. Having said that, this research would seem to confirm an earlier randomised, placebo-controlled, double blind study which gave HD subjects highly unsaturated fatty acids as part of their diet and was the first trial to show significant improvement of subjects[101]. The same authors found their results were consistent with a second placebo-controlled study of end-stage patients as well as their observations of a Huntington's transgenic mouse model. Strong evidence exists which favours the use of EFAs in normal brain health and since HD usually strikes its victim at a point in life when age may well be having a negative effect on brain function anyway, the use of EFAs ought seriously to be considered at as early a stage as is possible. Normal brain development is a complex interactive process dependent on a timely orchestration of external and internal inputs through sophisticated intra and intercellular signalling pathways in which EFAs play a pivotal role. The discovery of the essentiality of long-chain polyunsaturated fatty acids (PUFAs) was made in 1929 by Burr and Burr[102]. In the intervening years, science has shown that brain FA composition reflects dietary availability which indicates important implications for population health in general[103]. With aging comes a likely increase in reactive oxygen species (ROS) associated with a decline in membrane PUFA concentrations which is known to correlate with cognitive impairment. Other neurodegenerative disorders such as Parkinson's and Alzheimer's Disease appear to exhibit membrane loss of PUFAs. It would therefore seem reasonable to anticipate that an optimal diet, which containes a balance of omega 6 and omega 3 FAs, may help delay the onset of disease or indeed reduce the insult to brain functions in neurodegenerative diseases such as HD[104]. In the laboratory, dietary manipulations such as dietary supplementation with EFAs from conception onwards, have been found to both slow disease progression and increase survival in HD transgenic mice [105].

Creatine

Reports assert a positive role for supplemental creatine in the treatment of HD as it has been shown to be beneficial in cases of mitochondrial dysfunction and disruption of energy production [106,107]. This product is familiar in the field of sports nutrition where the creatine monohydrate form has become one of the most extensively studied and scientifically validated nutritional ergogenic aids for athletes. It has been found to increase high intensity exercise capacity and lean body mass during training and has earned the status of being a nutritional alternative to potentially dangerous anabolic drugs[108]. Although the effect of long term supplementation is still unknown, to date there is no scientific evidence to suggest that its use in the short or medium term has any detrimental effects on otherwise healthy individuals[109]. Biochemically, the energy supplied to rephosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP) during and following the use of muscle tissue is largely dependent on the amount of phosphocreatine stored in that muscle[110, 111] and as a result of this creatine has been evaluated as a potential therapeutic agent in a variety of medical conditions thought to benefit from its supplementation such as Alzheimer's, Parkinson's and HD[112]. Quality control in creatine supplements is of concern as contaminants such as dicyandamide and arsenic are by-products of unscrupulous commercial production [113]. However, creatine has been found to mediate remarkable neuroprotection in animal models of HD and no known drug, nutritional supplement or herb interactions have been recorded. Although there exists potential for its therapeutic application, an incomplete knowledge base still exists and its effectiveness and safety over prolonged periods of time should be defined.

The Role of Functional Testing

The ability of the nutritionist to create a personalised treatment plan based on a functional assessment of nutrient status holds the greatest promise for improving patient outcomes. A wide array of non-invasive functional tests are now available to health personnel which include relevant markers for energy metabolism, detoxification, oxidative stress, B vitamin and methylation status, AA and neurotransmitter turnover. The most sensitive and specific test for mitochondrial dysfunction is believed to be Urinary Organic Acid Analysis[114]. This test has traditionally been used to detect inborn errors of metabolism but two of the world's leading organic acid researchers believe that the clinical relevance of this test is an ability to detect dysfunction of mitochondrial energy production as well as the presence of functional

nutrient deficiencies and toxins that adversely affect detoxification pathways [114]. Urinary Amino Acid Profiling can elucidate the adequacy and balance of dietary protein as well as a person's susceptibility to an inflammatory response and oxidative stress. Taken in combination, these two tests alone could provide the nutritionist with the information required to design a protocol in cases of both pre-symptomatic and symptomatic HD where customised nutritional recommendations may aid patient compliance and outcome.

Conclusion

In conclusion, the past three decades of research have shown that the chemistry and function of both the developing and mature brain are influenced by nutrition and never more so than in the disease state. Years of concientious research have been an essential component of HD diagnosis and, as yet, the elusive potential cure. This study, although possibly restricted in terms of information resources, has confirmed that little research currently exists into the possibility that a carefully structured nutritional programme could have a beneficial effect on postponing both disease onset and phenoconversion [115] to the disease state. Researchers in the field of HD have understandably concentrated on unravelling the disease process which, to date, still eludes them. Most papers which touch on nutrition or food in relation to HD deal with hypercalorific diets and feeding methods which they believe may improve quality of life. The former would seem to contradict research which has found that dietary restriction along with environmental enrichment, in both animals and humans, can lead to a decrease in neurodegeneration and improvement in cognitive function[116,117]. Also, providing high carbohydrate/high fat foods in a bid to maintain or boost energy status could be contraindicated in a person with the htt gene who exhibits flawed TCA and ETC activity, and could cause an undesirable build up of lactate concentrations. Lactate is the end product of anaerobic glycolysis and is present in normal brain in barely detectable amounts. The amount of lactate measured in some patients with HD can be ten-fold above the baseline of normal controls and as such presents another significant area for further research in the pathogenesis of this disease[118] .

Functional testing could therefore become a useful tool in highlighting individual imbalances in metabolism and instrumental in nutritionists being able to strategically target those imbalances with positive outcomes. In the future, it would be extremely valuable to conduct nutritional trials with people already expressing full HD alongside people who are asymptomatic, and make observations on a longitudinal basis to record any changes in the

patients' wellbeing. The time involved to do this research, coupled with a Huntington candidate's understandable reticence to confirm diagnosis, would be obvious drawbacks. However, it is hoped that by this means a better future understanding of the intricacies of HD can lead to new therapeutic approaches. HD patients rarely conform to a textbook description and frequently require the availability of unique regimes tailored to individual needs provided by those well informed in the disease process. As a result of conducting this study it has become evident that the ultimate goal of care for HD patients should be to maximise their quality of life throughout the course of the disease. The author considers that a real opportunity exists for the role of nutrition in this paradigm through investigation by means of functional testing and the subsequent ability to tailor nutritional strategies accordingly. Nutritionists have the potential to promote and support a fragile metabolism under threat and are in a position to aim at postponing disease onset and to become involved in active disease management, thus complementing any current medical intervention in a multi-disciplinary approach.

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