Potential Benefits of Ameliorating Metabolic and Nutritional Abnormalities in People With Profound Developmental Disabilities

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ABSTRACT

BACKGROUND: People with profound developmental disabilities have some of the most severe neurological impairments seen in society, have accelerated mortality due to huge medical challenges, and yet are often excluded from scientific studies. They actually have at least 2 layers of conditions: (1) the original disability and (2) multiple under-recognized and underexplored metabolic and nutritional imbalances involving minerals (calcium, zinc, and selenium), amino acids (taurine, tryptophan), fatty acids (linoleic acid, docosahexaenoic acid, arachidonic acid, adrenic acid, Mead acid, plasmalogens), carnitine, hormones (insulinlike growth factor 1), measures of oxidative stress, and likely other substances and systems.

SUMMARY: This review provides the first list of metabolic and nutritional abnormalities commonly found in people with profound developmental disabilities and, based on the quality of life effects of similar abnormalities in neurotypical people, indicates the potential effects of these abnormalities in this population which often cannot communicate symptoms.

KEY MESSAGES: We propose that improved understanding and management of these disturbed mechanisms would enhance the quality of life of people with profound developmental disabilities. Such insights may also apply to people with other conditions associated with disability, including some diseases requiring stem cell implantation and living in microgravity.

KEYWORDS: Developmental disabilities, fatty acids, amino acids, minerals, nutrient deficiencies, stem cell transplantation, microgravity

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Introduction

William Harvey (1578-1657), who demonstrated how blood circulates, noted, "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her working apart from the beaten path . . ."[1]

Context

People with profound developmental disabilities have some of the most severe impairments seen in society, involving cognitive (IQ less than 20), communicative (nonverbal), and motoric function (impaired activities of daily living), with onset before the age of 18 years. Although they constitute a very small proportion of society, they are at increased risk for multiple medical problems,[2] including paralysis, epilepsy,[3] fracture,[4] inability to communicate, and malnutrition,[5,6] with significantly increased costs as a consequence.[7] Accelerated mortality[8] demonstrates that they face enormous medical challenges but are often excluded from scientific study.[9] Metabolic and nutritional rehabilitation has the potential to contribute to reduction in morbidity and mortality in which there are significant disparities compared with neurotypical people.[10]

We propose that people with profound developmental disabilities actually have at least 2 coexisting conditions: (1) the original disability, categorized by the cause,[11] such as congenital anomalies, syndromes, genetic diseases, inborn errors of metabolism, brain trauma, and autism and (2) a secondary layer of minimally documented and underexplored biochemical imbalances and nutritional processing issues, which this review summarizes. Accordingly, depending on yet-to-be-identified aspects of the disability (such as paralysis) or the degree thereof, any of the Opitz categories may be variably affected by the secondary layer. And, the elements of both layers must be identified and managed to optimize the person's quality of life.

Purpose of This Report

This review presents the first collection of articles on the metabolic and nutritional abnormalities commonly found in people with profound developmental disabilities. It is being offered to experts in nutrition and metabolism because an understanding of cutting-edge biochemistry is often necessary to explore secondary metabolic phenomena and to make clinical decisions which may remediate apparent deficiency states.

We propose that improved management of the secondary layer of biochemical and nutritional problems of people with profound developmental disabilities would be valuable despite formidable biological, ethical, methodological, and financial challenges.

Common Biochemical and Nutrient Deficiencies and Their Potential Consequences in This Population

These secondary nutrient-processing abnormalities and biochemical imbalances are commonly manifested as unexplained low or even high circulating concentrations of a nutrient or metabolite despite recommended dietary intake of that nutrient.[12,13]

In the following sections, we briefly summarize the evidence of documented and suspected abnormalities of fatty acids, amino acids, minerals, vitamins, and other nutrients as well as the potential consequences, based primarily on studies in neurotypical people (Table 1). The list, in roughly descending order starting with those abnormalities for which the most evidence exists, is not exhaustive. Lack of data prevents simple stratification by prevalence within the population of people with profound developmental disabilities, and age-of-onset has not yet been identified. Multiple coexisting abnormalities and imbalances are common in individuals in the authors' experience, and some have the potential to result in further impairment of cognition. In the references, human studies are cited except for animal or in vitro studies that provide mechanistic explanations.

Fatty acid abnormalities (wt%, as customarily expressed) are quite common in people with profound developmental disabilities. Linoleic and α-linolenic acids are essential fatty acids which, by definition, must be obtained from diet. Figure 1 displays a simplified schematic representation of the primary metabolites of these 2 fatty acids. Fatty acid sufficiency is crucial for brain function because 25% to 30% of brain tissue is made of fatty acids.[14]

Low circulating linoleic acid (C18:2n6) is seen in total fatty acids,[15] phospholipids,[16] and erythrocytes despite abundant linoleic acid intakes (4%-8.1% of energy). Mead acid (C20:3n9) may be elevated, suggesting frank linoleic acid deficiency. The reason for apparent linoleic acid deficiency in the context of dietary sufficiency, however, is not yet clear. Historically, it has been very difficult to induce linoleic acid deficiency through oral deprivation in healthy volunteers, but linoleic acid–deficient enteral formulas can induce deficiency.[17] Elevated concentrations of oleic (C18:1n9) and vaccenic (C18:1n7) acids are also seen. Vaccenic acid may be a cardiovascular risk factor[18] and is known to inhibit gluconeogenesis,[19] possibly providing a reason for the puzzling appearance of unexplained hypoglycemia that is occasionally seen. Low cell membrane linoleic acid adversely affects membrane structure, reduces availability of arachidonic acid as a substrate for phospholipids (which may impair neuroplasticity[20]), or may impair cardiolipin sufficiency, consequently interfering with electron transport.[21] Although impaired electron transport has adverse clinical effects in a variety of settings, its significance in this context is not known. Secondary distortions of the fatty acid profile which result from low linoleic acid undoubtedly have additional implications. It should not be overlooked that oleic acid is the primary energy source for resting muscle,[22] which may be especially problematic for individuals with paralysis.

Docosahexaenoic acid (DHA; C22:6n3) is the most abundant structural fatty acid in brain. Its status is marginal based on circulating concentrations and ratios of other crucial fatty acids such as arachidonic acid and docosapentaenoic acid n-6, a less functional molecule.[16,23,24] Human DHA status is the result of both diet and endogenous synthesis, and deficiency is associated with the risk of a variety of cardiac and mental health conditions. Unbalanced omega-6/omega-3 status and low DHA are associated with cognitive impairment in a study of children with intellectual disabilities,[25] worse outcomes in traumatic brain injury,[26] increased cardiovascular disease risk,[27] sudden death due to cardiovascular disease risk,[27] sudden unexpected death in epilepsy,[28] primary open-angle glaucoma,[29] and age-related macular degeneration.[30] There is evidence linking imbalances of these fatty acids in pregnant women with the risk of cerebral palsy.[31] Relationships between fatty acid status and cognitive impairment have also been demonstrated in neurotypical adults.[23,32–35]

Arachidonic acid (C20:4n6) may be elevated in circulation.[15,16] It is abundant in brain structure[36] and is the precursor for a large number of (mostly) inflammation-related cytokines. Adrenic acid (C22:4n-6) is an elongation product of arachidonic acid and is especially abundant in white matter. In people with profound developmental disabilities, we have observed clinically that adrenic and arachidonic acids tend to fall to statistically low levels when fish oil is given, as might be expected,[37] and trend toward normal when DHA alone is then given. Low plasma adrenic acid has been observed in autism in Japan,[38] where dietary n-3 polyunsaturated fatty acid (eicosapentaenoic acid and DHA) intake is relatively high.[39]

Low circulating red blood cell (RBC) plasmalogens[16] (16:0 dimethylacetal [DMA], 18:0 DMA, total 18:1 DMA) may result in impaired management of reactive oxygen species, alter cell membrane structure, and impair surfactant composition. Plasmalogens are unique glycerophospholipid molecules and constitute about 18% of the total phospholipids in cell membranes.[40] Because of the vinyl ether bond at the sn-1 position of the glycerol backbone, they are able to bind free electrons and thus terminate sequential free radical damage. Deficiencies are seen in many metabolic and inflammatory conditions, including primary open-angle glaucoma[29] and they may be an independent marker for Alzheimer disease, falling in circulation as cognition declines.[40,41] Oxidative stress and inflammation[42] may result in depletion.

Low circulating free fatty acids (unpublished , April 2005–April 2006) are likely the consequence of low lipolytic activity[43] due to decreased catecholamine activity consequent to prolonged recumbency. Free fatty acids, particularly as acyl-CoA derivatives, are necessary substrates for many metabolic fates of fatty acids. Low circulating concentrations have been associated with increased risk of senile cataracts.[44]

Table 1. Nutrients/metabolic processing abnormalities and systems potentially affected.

SIGN, SYMPTOM, SYSTEM	COGNITION	SEIZURES	SUDEP	TBI	PAIN	CEREBRAL PALSY	INFLAMMATION	BONE STRENGTH	BLOOD DISORDERS	CARDIAC ISSUES	MUSCLE STATUS	EYE ISSUES	IMMUNITY	OXIDATIVE STRESS	ENERGY METABOLISM
Nutrient															
Linoleic acid	X						X			X	X				X
Plasmalogens	X						X							X	
Free fatty acids												X			
DHA	X		X	X		X	X			X		X			
Arachidonic acid	X						X								
Taurine	X	X		X	X			X		X	X	X	X	X	X
Tryptophan	X				X			X		X					
IGF-1	X							X					X		
Protein turnover											X				
Methyl groups	X														
Carnitine	X	X				X				X			X		
Vitamin D	X				X		X	X		X	X		X		
Calcium								X							
Zinc								X					X		
Selenium														X	
Copper									X						
Nucleotides	X												X		
Phytochemicals							X	X		X				X	

Abbreviations: DHA, docosahexaenoic acid; IGF-1, insulinlike growth factor 1; SUDEP, sudden unexpected death in epilepsy; TBI, traumatic brain injury.

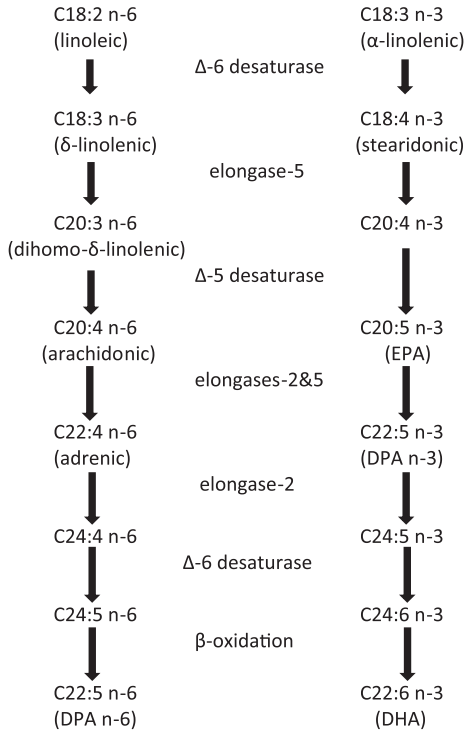

Figure 1. Simplified schematic representation of enzymatic cascade for the 2 essential fatty acids, in which elongases and desaturases are shared.

Low plasma taurine[45] is very common. Beyond infancy, taurine is not considered to be an essential amino acid. Although taurine is not part of protein structure, it is one of the brain's most abundant amino acids.[46] Deficiency in this context may be due to lack of cysteine dioxygenase activity due to muscle atrophy–related leucine deficiency,[47] vitamin B_6 deficiency (specifically, pyridoxal-5′-phosphate),[48] excessive excretion,[49] and/or conjugation.[50] In humans, taurine deficiency may increase the risk of seizures,[51] interfere with responses to spinal and head trauma,[52,53] increase pain,[54–57] reduce bone strength,[58] increase oxidative stress,[59] contribute to cataract[60] and retinal disease risk[61] (especially when vigabatrin is given[62]), increase the risk of chronic heart failure,[63] increase hypertension risk,[64] increase the risk of coronary heart disease in people with hypercholesterolemia,[65] modulate human arterial stiffness,[66] reduce protection from glutamate-induced apoptosis,[67] interfere with osmoregulation[68] (crucial as intracellular water is already low in people with paralysis[69]), interfere with β-oxidation of fatty acids by inadequately buffering intramitochondrial pH,[70] interfere with skeletal muscle contraction[68] and muscle mass,[71] modify immune responses,[72] and create a biochemical phenotype which resembles certain mitochondrial diseases such as MELAS (m.3243A > G; mitochondrial encephalopathy, lactic acidosis, and stroke) and MERRF (m.8344A > G; myoclonic epilepsy with ragged-red fibers).[73] It is our observation that taurine supplementation of enterally administered commercial formulas was started decades before these deficiency-related clinical risks were identified. Supplementation of enteral formulas is not universal at this time.

Low plasma tryptophan[74,75] is possibly related to diversion into the kynurenine/quinolinic acid pathway[76] or excessive peripheral serotonin synthesis. Adverse consequences may include reduced synthesis of a variety of proteins, impaired brain plasticity,[77] impaired bone strength,[78–80] increased pain during depression,[81] complications of complex regional pain syndrome,[82] increased susceptibility to delirium,[83] increased likelihood of subclinical pellagra[84] (dementia, diarrhea, and dermatitis are common in pellagra), increased risk of death due to cardiovascular disease,[85] and unexplained elevated blood serotonin (found also in autism[86]), each suggesting unbalanced tryptophan metabolism. Increased excretion of serotonin is also seen with −6° head-down-tilt bed rest studies used to estimate the effects of microgravity.[87] Other amino acids may also be low, including branched-chain amino acids (BCAAs), probably related to muscle atrophy due to paralysis because BCAAs comprise about one-third of the amino acids in muscle. Because leucine has signaling, especially for mammalian target of rapamycin complex 1 (mTORC1),[88] as well as structural roles, low circulating BCAA concentrations may have wide-spread ill-defined consequences.

Evidence of increased protein turnover manifested as elevated 24-hour urine 3-methylhistidine/creatinine ratios has been found. (Unpublished [1987, 1991] but demonstrated in neuromuscular disease,[89] possibly due to recumbency-related angiotensin II.[90]) This elevation is presumed to be derived primarily from muscle, but the rates of protein turnover in other tissues, including brain, are not known. Nevertheless, the resultant increased protein synthesis is likely to increase protein misfolding, a common feature of neurodegenerative disease, which disrupts cellular proteostasis, possibly compounding the disability.[91] In addition, mTORC1, which is sensitive to amino acid status, is intimately involved in proteostasis via complex responses.[92]

Low circulating insulinlike growth factor 1 (IGF-1)[74] has multiple potential adverse effects on bone integrity, stature, infection risk,[74] and cognition[93] and may increase the risk of postoperative delirium.[94] Insulinlike growth factor 1 may similarly be low due to recumbency-related excessive angiotensin II.[90,95]

Impaired methylation findings are based on elevated RBC mean corpuscular volume, elevated RBC folate, and other findings in people with cerebral palsy.[96] Defective methylation may have a profound effect on cellular activity and may be implicated in learning, memory, and age-related cognitive function decline.[97]

Low total and free circulating carnitine[45,98] may be related to medications, such as valproic acid, decreased muscle mass (as much as 95% of carnitine is stored in muscle), and to carnitine-free enteral feedings in children with epilepsy because 75% of carnitine is obtained from diet.[99] Because methylation is required for carnitine synthesis, some aspects of methyl group availability or disordered transmethylation may be present.

Low circulating 25-hydroxyvitamin D is common in some studies of people with profound developmental disabilities.[100,101] It may adversely affect fracture risk[4] and may contribute to a wide variety of human ailments[102] including cognitive impairment,[103] inflammation,[104] risk of cardiovascular disease,[101] risk of myopathy,[105] and chronic pain.[105,106] Vitamin D also regulates serotonin synthesis in the central nervous system, suggesting a wide theoretical range of clinical effects beyond those currently described. Deficiency appears to be a risk factor in autism.[107]

Calcium balance in this population was negative due to calcium malabsorption, as found in a balance study.[108] Calcium balance was achieved only after 150% of recommended daily allowance (RDA) for calcium was provided. Calcium malabsorption resulting in latent calcium deficiency may interfere with bone development. There is no simple laboratory method to determine the adequacy of dietary calcium in individuals, which seems to be necessary in this context.

Zinc balance was also negative due to zinc malabsorption, also found in a balance study.[108] Similar to calcium, zinc balance was achieved only after 150% of the RDA for zinc was provided. Deficiency may interfere with olfactory and gustatory sensations, immune function, and bone development and is associated with increased risk of pneumonia[109] and seizures.[110]

Low plasma selenium is manifested as slow responses to selenium repletion,[45] possibly prolonging free radical damage.

Low serum copper[111,112] is found in jejunostomy-fed people, as is common in people with profound developmental disabilities, in whom gastric and duodenal copper absorptive sites are bypassed. Copper deficiency may result in microcytic anemia, despite normal iron intake, neutropenia, neuropathy, and increased seizure risk.[110]

Nucleotides may be low[113] as they are not typically supplied in enteral feedings beyond infancy (human breast milk is rich in nucleotides) and may contribute to malabsorption,[114] impair cellular immunity,[115] and lower IGF-1 status.[116] Interestingly, Wurtman et al, by administering uridine and DHA, documented reversible brain biochemical and behavioral impairments associated with social isolation in rodents.[117–119] Enhanced cortical DHA and arachidonic acid as well as learning ability have also been shown in a rodent model given a dietary nucleotide mixture.[35] Although there is evidence that DHA status is impaired, the nucleotide status of people with profound developmental disabilities is not known. Socially isolating aspects of the lives of people with severe and profound developmental disabilities, whether related to living context, paralysis, communication barriers, or cognitive impairments, would be consistent with nucleotide imbalance.

Phytochemicals have been abundant in human evolutionary nutrition[120] but are not found in tube feedings, the consequences of which have not yet been explored in this context. In people with profound developmental disabilities, there is indirect evidence of increased oxidative stress manifested as low circulating uric acid[121] (circulating uric acid has antioxidant effects), low circulating total glutathione, and elevated urine erythronic acid (unpublished, November 1992–July 1993). We hypothesize that phytochemical deficiencies would result in increased oxidative stress, inflammation,[122] and other abnormalities.[123] Dried plums, commonly given as juice in people with profound developmental disabilities, have been shown to improve osteoporosis in neurotypical people.[124] Resveratrol, a trihydroxystilbene found in plant sources, is known to activate SIRT1 (silent information regulator 1) and subsequently peroxisome proliferator–activated receptor γ coactivator (PGC-1α), which enhances mitochondrial function in muscle and nervous tissues.[125] Resveratrol, curcumin, and other small molecules appear to reduce protein misfolding, as referred to above.[126] A variety of berries appear to improve cardiovascular risk factors.[127] Some anticonvulsants, which are administered to 75% to 90% of people with profound developmental disabilities, have been shown to increase oxidative stress in vitro, in animal models, and in humans.[128] Urinary dihomo-isoprostanes, which are oxidative stress–related metabolites of adrenic acid, are elevated in people with epilepsy.[129] Oxidative stress affects virtually all human conditions, so it is apparent that its influence on other conditions is not displayed in Table 1.

Methodological Challenges

The population under review presents a number of challenges for people conducting research. On one hand, neurotypical people are generally cooperative, verbally reveal symptoms which refine diagnostic possibilities in 80% to 90% of cases, are not considered to be in need of care unless they are symptomatic, often have an unifying diagnosis, self-select diets, give personal consent for scientific study, and are easy to sample.

On the other hand, people with profound developmental disabilities may not be able to cooperate, may be incapable of complaining, may have nonspecific symptoms, may require frequent physical and biochemical assessments to arrive at a diagnosis, may passively endure deficiency-related signs or symptoms, cannot make personal dietary choices, cannot give personal consent, and may have paralysis-related low muscle mass with consequent low urine creatinine, the internal standard for many urine assays.

Identification and management of multiple deficiencies or imbalances are also complex because of the following: (1) they are not easily identified because many pertinent metabolites are not assayed by commercial laboratories; (2) circulating imbalances may result from altered metabolism rather than simple deficiency, making direct repletion unwise or ineffective in some instances (as with tryptophan, which may result in interferon gamma–related overactivation of the kynurenine-quinolinic acid pathway[130]); (3) repletion may normalize the circulating concentration without elucidating the underlying cause of the deficiency state (as with taurine); (4) it may be necessary to

replete in a specific order of a yet-to-be-established hierarchy of biological systems, as occasionally seen in unexplained hypothermia in people with profound developmental disabilities, analogous to the need to optimize adrenal cortical status before treating the hypothyroidism found in hypopituitarism to avoid precipitating an overt hypoadrenal crisis[131]; and (5) clinical benefit may not be apparent until a crucial number of deficiency states or imbalances have been identified and properly managed.

Major philosophical and ethical issues complicate interpretation of evidence-based nutrition compared with evidence-based medicine.[132] Indeed, randomized controlled trials may not be possible for ethical reasons if the control group cannot be defined and then recruited in complex, multifactorial contexts when there are few subjects, as is common among people with profound developmental disabilities.

Multiple deficiencies or imbalances are analogous to a car with 4 flat tires: it will not roll properly until all 4 tires have been repaired. A mechanic, if blinded to the fact that all 4 tires are flat, may assume that the first tire repaired was inconsequential because the car will not roll normally. But if 3 tires are secretly repaired by someone else, the mechanic will assume that the fourth tire repaired was the sole source of dysfunction.

Similarly, the best seeds in the world will not grow well in an infertile field. Physicians who work in this discipline find that some drugs (anticonvulsants, antipsychotics, and postmenopausal anti-absorptive agents to reduce osteoporosis) and devices (vagal nerve stimulators for seizure control or baclofen pumps) may not function optimally, perhaps due to deficiencies and imbalances.

As a consequence, we have found it helpful to use the biochemical phenotype, which is common in managing inborn errors of metabolism, as a guide to understanding and managing complex deficiency states, to the extent that appropriate assays are available. Identifying, managing, and monitoring an individual's biochemical phenotypic status and correlating this status with close clinical observations are paramount.

Wider Significance

Improved metabolic rehabilitation of people with profound developmental disabilities may also provide insights which will increase the likelihood of functional outcomes in people with other complex conditions, following stem cell transplantation and, ironically, may increase the likelihood of survival when these problems arise in people who travel in space for long periods of time.

For example, innate[133] or implanted stem cells[134] may function suboptimally if the nutrient or biochemical milieu is deficient in some of the same nutrients found above.[135] This has been shown in a variety of settings for fatty acids involving DHA,[136] which influences multiple aspects of neural stem/progenitor cells. Similarly, taurine increases cell culture viability via multiple mechanisms, mediates proliferation of murine subventricular-zone neural stem/progenitor cells, and promotes differentiation of human mesenchymal stem cells into osteoblasts.[137,138] Alternatively, zinc stimulates DNA synthesis in mouse embryonic stem cells; zinc deficiency impairs proliferation of rat adult neuronal stem cells.[139–142] Tryptophan-kynurenine pathway abnormalities adversely affect progenitor cells.[143] Other examples include the following: choline, which influences methylation-related fetal progenitor cells[144]; methionine, which is crucial for human pluripotent stem cell survival and differentiation[145]; dietary methionine/cysteine proportions, which moderate myogenic stem cell differentiation in chickens[145,146]; reactive oxygen species, which are related to mitochondrial dysfunction due to age-related sirtuin-3 deficiency[147]; and folic acid, which stimulates transplanted neural stem cell proliferation after middle cerebral artery occlusion in rats and induces differentiation of neural stem cells into neurons in rats.[148,149] Neurotypical adults with acute myeloid leukemia have increased morbidity and mortality associated with broad indices such as body mass index and weight loss during hematopoietic stem cell transplantation.[150] Management of nutritional deficits, such as found in people with profound developmental disabilities, may be pertinent.

Interestingly, short-term earth-bound and space-based studies show that the physiologic state of many recumbent people with profound developmental disabilities is similar to that experienced in microgravity[151,152] in which there are cephalic fluid shifts,[153] muscle atrophy (sarcopenia), oxidative stress,[144,154] calcium malabsorption,[155] and bone loss.[154,156,157] Functionally, there are alterations in fine motor control, higher cognitive activities such as executive function, and spatial working memory,[152] all of which would be of concern for people with preexisting disabilities involving brain function. Fatty acid abnormalities are also found, including a dramatic decline in total red blood cell omega-3 concentrations in rodents (100- to 150-day flights),[156] decreased total red blood cell linoleic acid (C18:2n6) and arachidonic acid (C20:4n6) concentrations in human extravehicular simulations,[158] and reduced bone mineral density loss associated with fish consumption after short-term space flight in humans.[159] Although the comparison is imperfect, people with lifelong severe paralysis, as commonly seen in people with profound developmental disabilities, may represent the only available human nutritional model for long-term space travel, an uncharted quest.[160] Therefore, it may be necessary to better understand and remedy the abnormalities of this model before safe, prolonged space travel can be expected. Sophisticated analytical capabilities or appropriate support vehicles may be necessary on Mars-bound flights. Investigation of the impact of these nutritional aberrations on people with profound developmental disabilities may have benefits well beyond their direct clinical care.

Furthermore, the status of stem cells and microgravity (and simulated microgravity) have been linked through many

observations of the adverse effects of microgravity on multiple stem cell lines,[161] in the midst of which abnormalities of the nutritional and metabolic milieu may be a complicating factor.

At present, the justification for correcting deficits and imbalances is reminiscent of the practice of screening for iron deficiency anemia during infancy, which began in the 1920s.[162] Although early descriptions and interventions for iron deficiency anemia were imprecise and did not meet the standards of our day, the association between iron status and health in infancy was nevertheless established by those efforts. It took many decades before additional benefits of iron deficiency prevention were documented for emotional health, social function, behavior, sleep, motor function, and cognition among children and young adults.[163] Modern research methods, with appropriate adaptations, have the potential to clarify and perhaps improve these issues in people with profound intellectual disabilities through sustained efforts.

Conclusions

This review summarizes emerging evidence of underrecognized biochemical abnormalities of nutrient processing and imbalances involving fatty acids, minerals, and amino acids. Based on neurotypical people, these abnormalities are likely to have adverse effects on the well-being, function, longevity, and care costs of people with profound developmental disabilities.

Similar to William Harvey's unbeaten path, the clearer course toward general knowledge may lie through the forests of intellectual disabilities. Consequently, better understanding and management of nature's outlier physiologies may provide opportunities for integration of research efforts and enhance the health of other individuals, whether their disabilities are earth bound or microgravity induced.[151,164]

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