The importance of nutrition for cognitive development of children with down syndrome

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THE IMPORTANCE OF NUTRITION FOR COGNITIVE DEVELOPMENT OF CHILDREN WITH DOWN SYNDROME

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ABSTRACT

Down syndrome as the most common genetic disorder caused by excess chromosome on the 21st pair causes a number of phenotypic, psychomotor and cognitive specificities that are associated with excess genetic material. Depending on the intensity of gene expression, there are brain abnormalities of varying intensity such as differences in brain size and appearance, disruption of proteins crucial for neuromorphogenesis and optimal functioning of brain cells, which ultimately causes a number of conditions such as neurodegenerative diseases, oxidative stress, dendritic branching and intellectual disabilities. Excess genetic material in children with Down syndrome does not define special requirements regarding eating habits, however its overexpression very often causes conditions that require special dietary intervention. From an early age, feeding problems can be caused by hypotonia. Besides, sensory sensitivity to a certain consistency and texture of food is expressed, which leads to a deficient intake of nutrients through diet necessary for cognitive development. Numerous studies have focused on the importance of dietary intake of certain nutrients to improve the cognitive development of children with Down syndrome. Of exceptional importance for brain development is the intake of ω-3 fatty acids, iron, zinc, iodine, vitamin B12 and folic acid. The aim of this paper is to provide an overview of research on the importance of nutrient intake crucial for the development of cognitive abilities through diet in children with Down syndrome.

Keywords: Down syndrome, trisomy 21, nutrition, cognitive development

INTRODUCTION

Down syndrome is caused by trisomy of the whole or a part of 21st chromosome. It is the most common cause of mild to moderate intellectual disability and affects from one in 319 to one in 1000 liveborn infants, although this prevalence varies between countries because of differences in maternal age and prenatal screening (Park and Chung, 2013; Nordstrom, 2020).

Table 1. Possible physical features and congenital condition associated with Down syndrome (Eckdahl, 2018)

Physical features	
Head	Small, shortened skull that is flattened on the back, sloping forehead, missing or underdeveloped sinuses.
Eyes	Upward slanted and wide-set eyes, epicanthal folds, Brushfield spots.
Ears	Smaller ears with extra folds, ears set lower on the head.
Nose	Smaller nose, flattened nasal bridge.
Mouth	Smaller mouth, large tongue that tends to stick out more often, undersized teeth, crooked teeth, irregularly shaped teeth.
Hands	Broad hands, only one crease across the palm, short fingers, curved fifth finger.
Feet	Larger gap between the first and the second toe.
Limbs	Short and stocky arms and legs with hyperflexible joints.
Body	Short stature, shorter and wider neck, protruding stomach.
Congenital condition	
Heart	Septal defects (atrial septal defect, ventricular septal defect, atrioventricular septal defect), patent ductus arteriosus, tetralogy of Fallot.
Vision	Refractive errors, cataracts, amblyopia, blepharitis, glaucoma.
Hearing	Hearing loss (conductive and sensorineural), glue ear, otitis media.
Musculoskeletal	Hypotonia, ligamentous laxity, atlantoaxial instability, hip abnormalities, kneecap instability, flat feet.
Digestive	Hirschsprung disease, tracheoesophageal fistula, esophageal atresia, duodenal atresia, imperforate anus, gastroesophageal reflux disorder.
Immune	Hypothyroidism, celiac disease, respiratory infections.

Children with Down syndrome show large variability in physical features and congenital condition (Table 1.) because some have mild symptoms and complications, whereas others are more severely affected. This variability also relates to the risk of health and cognitive problems associated to poor nutrition in early age. Attention to nutritional intake and status is important for children with Down syndrome because some features and comorbidities have nutritional

implications and consequences (Freeman et al., 2008; Wong et al., 2014; Ergović Ravančić and Obradović, 2021).

Early life experiences have an impact on child health and development. Increasing evidence suggest that multidisciplinary aproach to children development needs to begin in early childhood because cognition related behaviors have early origins. Regardless of weight status, poor diet and activity levels may also have consequences for current and future health and development of children with Down syndrome. The early childhood years are a time for rapid and robust growth in cognitive development, but also a time of great vulnerability in this regard (Tandon et al., 2016).

Cognitive development is a complex, multidimensional set of abilities. In addition to the fundamental complexity of mental functions involved in any cognitive task, intellectual performance in specific test conditions depends on several factors including individual skills, motivation, general excitment, prior learning, fatigue and time of a day (Bhatnagar and Taneja, 2001). Given the number and complexity of factors than can affect cognitive performance at any given time, it is not surprising that very few nutritional effects on cognition have received scientific support. In this paper we consider the beneficial effects of nutrients from diet to improve the cognitive performance.

NUTRITION AND COGNITION

Cognitive development involve several of mental activities related to information storage and processing: attention, memory, language, learning, decision making, and problem solving. (Bhatnagar and Taneja, 2001; Lozoff and Georgieff, 2006).

Structural organization of the brain implies neurons who work on specific subsets of cognitive functions in a coordinated manner and within a region or structure. Myelin-coated neurons transmit electrical signals in single, double, or multiple directions, using neurotransmitters to communicate and interact (Figure 1). Between structures, nerve fibers tracts allow different regions to coordinate in the higher orders of cognitive function. The combination of the neural cell functions and the structural organization enables the higher order of cognitive functions.

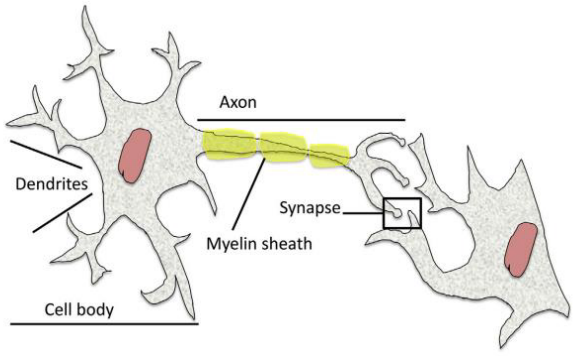

Figure 1. Structure of a neuron (Mehedint and Gulledge, 2014)

Nutrition as connection between nutrients and health, should provide the building blocks needed to build and maintain the structure of the central nervous system and function. There are five main classes of nutrients: proteins, fats, carbohydrates, minerals and vitamin. Insufficient amounts of any of these nutrients have been associated with various diseases (Bhatnagar and Taneja, 2001; Lozoff and Georgieff, 2006; Mehedint and Gulledge, 2014). Intellectual disability occurs when a child fails to fully develop the intellectual capacity to think, reason, learn, and understand. Children with an intellectual disability also have problems learning adaptive behavior, which encompasses the social and practical skills needed for everyday living. Intellectual impairment varies among children with Down syndrome. It ranges from severe intellectual impairment that makes people fully dependent on caregivers, to mild effects that enable people to think and learn at levels that enable them to pursue higher education, retain a job, and live independently (Stagni et al., 2015).

It's assumed that diet can play a key role in brain development and thus intellectual functioning. The brain, in a similar way to the rest of the body, need proteins, fats, carbohydrates, vitamins and minerals that are all ingested through food for growth and functioning. As the brain develops faster than the rest of the body, it is obvious to consider whether a lack of nutrition at a critical stage of development can lead to permanent changes in brain structure and functioning. In addition, the brain is the most metabolically active organ in the body, yet it has very limited stores of energy, so it relies on the diet for a continuous supply of glucose. Similarly, the minute-to-minute functioning of the brain requires an adequate supply of micronutrients that act as co-enzymes, or form structural parts of the enzymes required for optimal metabolic activity (Benton, 2005; Benton, 2010).

Vitamins, minerals, and antioxidants from the diet are important cofactors in many biochemical processes throughout the body. The presence of an extra copy of chromosome 21 in Down syndrome causes an overexpression of genes located on this chromosome and further metabolic changes, leading to increased levels of oxidative stress and several abnormalities in metabolism (Lima et al., 2010).

NUTRIENTS FOR IMPROVE THE COGNITIVE DEVELOPMENT

Studies have shown that the maturation of specific brain areas during childhood is associated with development of specific cognitive functions such as language, reading and memory (Nagy et al., 2004; Giedd et al., 2010). Since rapid brain growth occurs during the first 2 years of life (by the age of 2 the brain reaches 80 % of its adult weight), this period of life may be particularly sensitive to deficiencies in diet (Bryan et al., 2004).

ω-3 fatty acids

Dietary lipids are essential sources of metabolic energy, substrates for synthesis of active compounds, component of lipoprotein particles, and carriers for lipid soluble compounds. They participate in cell signaling and take active part in regulation of

gene expression. They are integral part of cellular membranes and precursors for bioactive compounds modulating a wide variety of biological functions.
Fatty acids are a part of lipids, which can be broken down into saturated and unsaturated acids. Eicosapentanoic acid (EPA) and decosahexanoic acid (DHA) are essential polyunsaturated lipids with an omega-3 desaturation that cannot be made in humans (Youdim et al., 2000).
In recent years, there has been an increasing interest in the effect of essential fatty acids, especially long chain polyunsaturated fatty acids, on cognitive brain development. 60 % of the dry weight of the human brain are lipids, of which 20 % are DHA and arachidonic acid (AA; an omega-6 fatt acid) the two core fatty acids found in gray matter (De Souza et al., 2011).
The supply of omega-3 fatty acids, including DHA and EPA, is frequently inadequate for children as well as for adults despite the knowledge that they play a central functional role in brain tissue. They are not only the basic components of neuronal membranes, but they modulate membrane fluidity and volume and thereby influence receptor and enzyme activities in addition to affecting ion channels. Essential fatty acids are also precursors for active mediators that play a key role in inflammation and immune reaction. They stimulate the growth of the neuronal and dendritic spine and synaptic membrane synthesis, so therefore influence signal processing and neural transmission. In addition, essential fatty acids regulate gene expression in the brain (Schuchardt et al., 2010; De Souza et al., 2011; Prado and Dewey, 2014). Zmijewski et al. (2015) presented results of research in which omega-3 containing fish oil with other healthy nutraceuticals can modestly suppress regulator of calcineurin 1 levels in mice with Down syndrome and supported the idea that fish oil could be an effective and cheap agent to treat genetically defined pathologies like cognitive decline.

Iron

Iron is a very important mineral for human health, primarily due to its structural and chemical roles in the heme rings of hemoglobin and cytochrome P450 and in various other structural and chemical roles in metabolic proteins (Carlson et al., 2007). Heme iron, in particular, is involved in the regulation of various cellular functions, such as respiration, proliferation, and differentiation. Iron also modulates specific brain functions by increasing the release and turnover of dopamine and other neurotransmitters. The brain is arguably the most metabolically active organ in the body and its internal concentration of iron is exceptionally high particularly during the phases of neurodevelopment due to iron's role in myelinogenesis (Barone et al., 2018).
Iron deficiency with or without anemia early in life has been associated with adverse long-term outcomes. Studies have shown that early iron deficiency affects neuronal function and myelination and is associated with behavioral abnormalities and, if left untreated, can lead to reduction cognitive functions and changes in behavior and mood. Therefore, it is crucial to recognize and treat iron deficiency for at an early stage of brain development (Hart et al., 2020).

Zinc

Zinc deficiency slows growth because it is involved in the activity of more than 200 enzymes, especially those associated with the synthesis of RNA and DNA.
In addition, zinc plays a role in neurogenesis, maturation, and migration of neurons and in synapse formation that are centrally involved in learning and memory (Black, 2003).
Experimental and clinical studies have found that zinc metabolism is altered in individuals with Down syndrome. Lima at al. (2010), reported that adequate zinc intake was observed in 40 % of children with DS and in 67 % of the control group and zinc concentrations were significantly lower in plasma and urine and higher in erythrocytes of children with Down syndrome. Many symptoms of children and adults with Down syndrome are conseqences by an excessive synthesis of multiple gene products, including an increase in the intracellular activity of copper-zinc superoxide dismutase due overexpression of genes present on chromosome 21. Zinc stabilizes the 3-D structure of superoxide dismutase and thus reduces the imbalance (Lima et al., 2010).

Iodine

Iodine deficiency is very often described as greatest single cause of preventable brain damage and intellectual disabilities, because iodine is necessary for the synthesis of thyroid hormones which in turn act by regulating the metabolic pattern of most cells of the organism. It also plays a crucial role in the process of early growth and development of most organs, especially the brain, which occurs in human subjects during the fetal and early postnatal life. Consequently, iodine deficiency, if severe enough to affect thyroid hormone synthesis during this critical period, will result in hypothyroidism and brain damage (Delange, 2000; Prado and Dewey, 2014).

Vitamin B12

Association between vitamin B12 and cognitive development has been mainly observed in infants born of vegetarian/vegan mothers or mothers on a macrobiotic diet. These diets can result in vitamin B12 deficiency, as vitamin B12 is largely found in animal products. Vitamin B12 deficiencies in infants included a variety of abnormal clinical and radiological signs such as: hypotonic muscles, involuntary muscle movements, apathy, cerebral atrophy, and demyelination of nerve cells (Louwman at al., 2000; Nyardi et al., 2013).
Vitamin B12 plays a key role in normal brain development and function and is required for enzyme methionine synthase, which is necessary for the synthesis of methionine who is the major methyl group donor used in human methylation reactions, including methylation of DNA and RNA. Deficient methylation reactions in the central nervous system can impair the methylation of myelin basic protein in the central as well as peripheral nervous system. The production of myelin is a key component of brain development from gestation, throughout childhood and well into

middle age. The myelination of the brain is of importance for multiple brain systems and is highly related to neurodevelopment and subsequent cognitive functioning.
Vitamin B12 also serves as a cofactor in numerous catalytic reactions in the human body, which are required for neurotransmitter synthesis and functioning. Vitamin B12 deficiency may cause pernicious anemia with similar effects on cognitive development and functioning as anemia caused by iron deficiency. Vitamin B12 deficiency can also result in neuropathy through degeneration of nerve fibers and irreversible brain damage (Winje et al., 2018).

Folic acid

Folates are water soluble vitamins that serve as coenzymes in a variety reactions, including de novo nucleotide biosynthesis and conversion of homocysteine to methionine which is required for various methylation reactions. Deficiency of folate results in a different clinical features like cytopenias (including megoblastic anemia), weakness, fatigue, headache, irritability, as well as gastrointestinal symptoms including nausea, vomiting, and mucosal aphthous ulcerations (Funk et al., 2020). Numerous enzymes involved in folate transport and metabolism are encoded by genes located on chromosome 21 and represent a potential mechanistic basis for folate dysregulation in children with Down syndrome.
Besade potential genetic causes of metabolic folate dysregulation in children with Down syndrome, non-genetic factors such diet, gender, and age must be considered because they must fully satisfy their folate needs through their diet since they lack the enzymatic machinery necessary to synthesize their own (Pfeiffer et al., 2012). Black (2008) explained two mechanisms for influence of folate and vitamin B12 deficiency on the brain: by disrupting myelination or influencing the inflammatory process.

CONCLUSION

Down syndrome is a condition characterized by an excess of genetic material on 21st pair of chromosomes. Many enzymes that are encoded on the extra 21st chromosome are known to be actively transcribed, which results in overexpression of many enzymes. Genetic overexpression of enzymes leads to overconsumption of their enzymatic substrates and overproduction of their metabolic end-products. Ultimately, children with Down syndrome have different nutrient needs and are often deficient which negatively affects on cognitive development. The majority of studies, which have investigated the association between nutrition and cognitive development, have focused on individual micronutrients but individuals consume combinations of food and poor overall diet can cause multiple macro-and micronutrient deficiencies and imbalances. If an overall healthy diet synergistically enhances cognitive development in children, then public health interventions should focus on the promotion of overall diet quality rather than isolated micronutrients or dietary components consumed by children.

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