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REVIEW ARTICLE

DOWN SYNDROME – GENETIC AND NUTRITIONAL ASPECTS OF ACCOMPANYING DISORDERS

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ABSTRACT

Down syndrome (DS) is one of the more commonly occurring genetic disorders, where mental retardation is combined with nutritional diseases. It is caused by having a third copy of chromosome 21, and there exist 3 forms; Simple Trisomy 21, Translocation Trisomy and Mosaic Trisomy. Symptoms include intellectual disability/mental retardation, early onset of *Alzheimer's* disease and the appearance of various phenotypic features such as narrow slanted eyes, flat nose and short stature. In addition, there are other health problems throughout the body, consisting in part of cardiac defects and thyroid function abnormalities along with nutritional disorders (ie. overweight, obesity, hypercholesterolemia and deficiencies of vitamins and minerals). Those suffering DS have widespread body frame abnormalities and impaired brain development and function; the latter leading to impaired intellectual development. Many studies indicate excessive or deficient nutrient uptakes associated with making inappropriate foodstuff choices, food intolerance, (eg. celiac disease) or malabsorption. DS persons with overweight or obesity are linked with a slow metabolic rate, abnormal blood leptin concentrations and exhibit low levels of physical activity. Vitamin B group deficiencies and abnormal blood homocysteine levels decrease the rate of intellectual development in DS cases. Zinc deficiencies result in short stature, thyroid function disorders and an increased appetite caused by excessive supplementation. Scientific advances in the research and diagnosis of DS, as well as preventing any associated conditions, have significantly increased life expectancies of those with this genetic disorder. Early dietary interventions by parents or guardians of DS children afford an opportunity for decreasing the risk or delaying some of the DS associated conditions from appearing, thus beneficially impacting on their quality of life.

Key words *Down syndrome, intellectual disability, mental retardation, Alzheimer's disease, nutrition.*

STRESZCZENIE

Jednym z częściej występujących zaburzeń genetycznych przebiegających z jednoczesnym występowaniem upośledzenia umysłowego i chorób żywieniowozależnych jest zespół *Downa* (ZD). Związany on jest z potrojeniem materiału genetycznego na 21 chromosomie. Występuje w trzech odmianach (trisomia prosta, trisomia translokacyjna i mozaicyzm). Charakteryzuje się: opóźnieniem umysłowym, wczesnym występowaniem choroby *Alzheimer'a*, występowaniem specyficznych cech fenotypowych (np. wąskie, skośne oczy, mały, płaski nos, niski wzrost), występowaniem wielopoziomowych zaburzeń organizmu (m.in. wady serca, zaburzenia gospodarki hormonalnej tarczycy) oraz chorób dietozależnych (nadwaga, otyłość, hipercholesterolemia, niedobór witamin, składników mineralnych). U osób z ZD występują rozległe zaburzenia w budowie, funkcjonowaniu i rozwoju mózgu, co skutkuje upośledzeniem rozwoju umysłowego. Liczne badania wykazują nadmiary oraz niedobory składników odżywczych związane z nieprawidłowym doborem produktów żywnościowych, występowaniem nietolerancji pokarmowych (celiakia) lub zespołem złego wchłaniania. Występowanie nadwagi i otyłości wśród osób z ZD łączy się ze spowolnionym tempem przemiany materii, nieprawidłowym stężeniem leptyny we krwi, niską aktywnością fizyczną. Niedobór witamin z grupy B oraz nieprawidłowy poziom homocysteiny we krwi u osób z ZD wpływa na spowolniony rozwój intelektualny. Niedobór cynku przyczynia się do niskiego wzrostu, zaburzeń gospodarki hormonalnej tarczycy oraz zwiększonego apetytu spowodowanego nadmierną jego suplementacją. Postęp nauki, prowadzenie badań związanych z diagnozowaniem i zapobieganiem chorób towarzyszących zespołowi Downa znacznie zwiększa długość życia osób z tą dysfunkcją genetyczną. Wczesna interwencja żywieniowa ze strony rodziców i opiekunów dzieci z ZD daje możliwość zmniejszenia ryzyka lub opóźnienie występowania niektórych współistniejących chorób, co wydatnie poprawiłoby jakość życia osób z zespołem *Downa*.

Słowa kluczowe: *zespół Downa, opóźnienie umysłowe, choroba Alzheimer'a, odżywianie*

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INTRODUCTION

The *Down* syndrome (DS) genetic disorder occurs in 1:600-700 newborns and is caused by over-expression of chromosome 21, where instead of two there are three copies. Many conditions are associated with DS such as metabolic disorders, tissue dimorphism, internal organ abnormalities, intellectual disabilities and characteristic phenotype features [28, 36]. Elucidating the genetic and nutritional factors that determine DS, provides an opportunity for developing new treatments for either decreasing or eliminating the risk of the conditions accompanying this disorder, together with improving health status and quality of life.

CHARACTERISTICS OF DOWN SYNDROME

DS is a disorder of development arising from incomplete embryogenesis as a result of an additional chromosome 21 copy in the karyotype. This extra chromosome is derived from an over-expression of genetic material due to a tripling of the number of genes. This phenomenon produces structural and functional disorders of the Central Nervous System (CNS), cardiovascular defects, dysfunction of the musculo-skeletal system, digestive system disorders as well as metabolic disorders, nutritional deficiencies, abnormal immune function, endocrine disruption (hypothalamic-pituitary-thyroid axis) and intellectual disabilities. DS children have impaired cognitive abilities and in most cases belong to those with mild-moderate intellectual disability. Late development at multiple levels is observed with impediments in speech, memory, perception and social/societal integration. Those with DS are vulnerable to degenerative changes in the brain that can be modest to severe. Such changes are due to oxidative damage to cells and tissue. Enzymatic disorders lead to excessive activity of peroxidases; that are linked to over-expression of the SOD-1 gene on chromosome 21. Structural dysfunctions of the mid-brain result in abnormalities for initiative taking and attention. Morphological anomalies in the sensory and association areas of the pre-frontal lobes result in impaired short--term memory and sense-associated cognitive abilities. Structural defects of the hippocampus cause long-term memory disorders. Such degenerative changes in the brain can occur singly or collectively and affect general body development in DS persons.

Brain pathologies in structure and function also result in discordant and late psychomotor development where there is a lack of coordinated motor movement and abnormal posture and locomotion [21, 36, 41]. One can distinguish between 3 forms of DS, namely Simple Trisomy, Translocation Trisomy and Mosaic Trisomy. In the former, the body's cell nuclei have 47 chromosomes which include 3 pairs of chromosome 21. This arises during formation of reproductive cells (oocytes, spermatocytes) and depends on abnormal chromosome separation at the first or second meiotic division leading to a doubled chromosome 21 in these cells; it occurs mostly in the oocytes for 95% cases. Karyotypes for girls are 47, XX, +21 and 47, XY, +21 for boys. Simple Trisomy in fact constitutes the most common form of DS in children and occurs at rates of 90-95%. Translocation involves transferring a chromosome fragment to another. In DS such translocation occurs between chromosomes 14 and 21, 21 and 22 and 22 and 21 which occur at rates of 5-6% of all DS cases. The karyotypes for girls are 46, XX, der (21;21), +21 or 46, XX, der (14;21), +21 and for boys 46, XY, der (21;21), +21 or 46, XY, der (14;21), +21.

Mosaic Trisomy occurs when the extra chromosome 21 is present in some, but not all cells, of the individual (ie. different karyotypes; normal and trisomic). It appears in 2-3% DS cases [36]. Three sub-divisions of Mosaic Trisomy are found; single cell type (composed of normal and trisomic cells), Tissue Mosaic Trisomy (tissues affected by the chromosome 21 trisomy) and chimerism (where two fertilized eggs are fused together into a whole giving rise to a single organism; where either or both eggs are affected by mosaicism) [45].

Dysmorphic features of DS affect whole body function and play a significant role in screening and

Table 1. Dysmorphic features in *Down* syndrome according to *Sadowska* et al. [36]

Body part	Morphological feature
Head	Small sized, anterior-posterior shortened, occipital region flattened and hair that is smooth, sparse and straight.
Face	Flat, round and slightly widened.
Eyes	Narrow and slanted palpebral fissures, epicanthic fold, Brushfield spots on the iris (small white spots), hypertelorism and frequent vision defects (myopia, cataracts)
Nose	Small, flat, short, with a wide thimble and constricted nasal passages
Ears	Small, deformed, low-set, upper part of ear sometimes collapsed and narrowed auditory canals.
Mouth	Thick cracked lips, receding lower lip, protruding tongue, often geographic and flaccid jaw muscles along with the tongue that causes mouth to be open
Palate	Narrow and high-arched; gothic style
Teeth	Misshaped and abnormally apart.
Neck	Short, broad with a skin fold.
Limbs	Wide, short hands and feet, palmar and sandal crease, clinodactyly, syndactyly, short upper and lower limbs in proportion to the body.
Skin	Rough, dry, marbled, bright and irritant sensitive.

diagnosis. They are mostly concerned with the face, eyes, ears, nose and limbs (Table 1). Each DS child possesses a unique set of phenotypic traits, however most children have similar morphological features.

Two forms of metabolic syndrome can be discerned from clinical observation; thyroid or pituitary type. Characteristics of the former are being stocky, clumsy and having bony posture, short stature, overweight, delayed bone maturation, apathy, dementia, mild nature, liking for music, hard skin and a yellowed tongue that is thick, long and broad. The hair is also straw coloured, the voice low and there is a tendency for being constipated. In children hypothyroidism is observed. The features of the pituitary type are short stature, underweight, slender bones, slim figure, accelerated bone maturation, hyperactivity, destructive behaviour, thin subcutaneous tissue, blood vessels prone to rupture, thin and sparse hair, tendency for alopecia and a high-pitched voice [22, 36, 47, 48, 51].

NUTRITIONAL PROBLEMS IN DOWN SYNDROM

Gastrointestinal tract abnormalities appear in 12% DS children and most commonly consist of; duodenal atresia, Hirschprung disease, trachea-oesophageal fistula, pyloric stenosis, annular pancreas and anal/rectal atresia. Also present are defects in the oral cavity that include delayed or atypical tooth eruptions, angenesis (congenital absence of teeth) and malocclusion. There is also a tendency for tooth decay and periodontal disease [31].

DS children exhibit feeding difficulties like in chewing and swallowing food boluses, inadequate nutrition and an inappropriate dietary calorific intake. Because of the numerous body defects, such children display low physical activity levels leading to reduced daily calorific requirements as compared with their healthy peers. Studies also show that DS children prefer consuming foodstuffs made of simple carbohydrates in their diets and those that are easy to chew and swallow. Fresh fruit and vegetables rarely feature in their diets due to difficulties in eating and by being rejected by these children. This leads to various nutritional deficiencies and a lack of regulating dietary ingredients as well as low dietary fibre intakes.

A consequence of these deficiencies gives rise to constipation and slow intestinal peristalsis. Many findings indicate overweight and obesity in DS children, together with abnormal lipid metabolism and Type II Diabetes [12, 24, 36, 42, 52]. DS children are frequently also born premature with low body mass and in adulthood, they have short stature as well as over half ending up being obese. The many defects seen in the gastro intestinal system coupled with its slow development rate (eg. the delayed coming-through of milk teeth) result in deficient uptakes of nutrients because solid foods are eaten at a later age, than is normal, when introduced into the diet. Short stature, lowered immunity and hypothyroidism are linked with dietary supplementation with zinc, which increases DS children's appetite. This taken with the particular and untoward dietary choices made, thus result in an increased risk of overweight and obesity [1, 13]. Studies by *Soler et al*. from Spain, found that the majority of subjects (n=38 with DS, aged 16-38 years) could be defined by their BMI, overweight and obesity. Serum glucose and cholesterol fraction concentrations were within normal. Levels of vitamin C and zinc in serum were lower-borderline normal.

A previous survey has demonstrated reduced dietary intakes of protein, fats, fibre and some vitamins and minerals (vitamins A, B_2, CX, sodium, potassium, calcium, phosphorus and iron) in DS subjects [43]. A similar study by *Samarkandy et al.* conducted in Saudi Arabia compared nutritional status between n=108 DS children and their siblings (n=113), aged 5-12 years and found higher rates of overweight and obesity in those with DS as well as the reduced aforementioned components of dietary intakes [28, 42]. Another study on nutritional status was performed by *Abdallah* et al. that investigated anthropometric parameters (height, body mass, BMI), diet (24 hour food survey) in children and adolescents (n=30, aged 6-18 years) suffering from DS; they also found overweight and obesity in more than half of their subjects. This nutritional survey showed excessive dietary intakes of carbohydrate, protein and fats compared to controls. In addition, deficient intakes of vitamins and minerals were observed (vitamins A and C along with calcium and zinc). The daily calorific dietary values were also excessive. The study recommends that healthy eating habits should be taught, together with adopting a balanced diet for the youngest children with DS, as they are most prone to suffer from overweight, obesity and a slow metabolic rate.

DS children have a shorter stature than their peers that is caused by deficiencies in growth hormone and IGF-1 as well as zinc. They also had deficiencies in vitamins A, C and of the B-group along with zinc, selenium, magnesium and manganese [1]. A Greek study by *Grammatikopoulou* et al. on nutritional status (body mass, height, skin-fold fat, BMI, and BHR) and diet (24 hour food survey) of 18 girls and 16 boys aged 2-18 years found excessive intakes of carbohydrates (mostly straight chain) that correlated with high body fat levels. Also seen were deficiencies in vitamins and minerals (vitamin E, calcium, zinc, selenium and iodine). Rates of DS subjects with overweight or obesity rose with age and the subject group showed low levels of physical activity resulting from both physical and mental

limitations. According to the authors, dietary excesses and deficiencies in these subjects arise from making inappropriate choices of foodstuffs that coincide with the children's preferences.

Educating parents of DS children in nutrition and restricting certain foodstuffs from their diet may reduce the risks of obesity in later life [14]. Studies by *Chad* et al. on 18 DS subjects showed a positive correlation between a slow metabolic rate and rates of overweight and obesity. Dietary deficiencies of nutrients were also observed (including iron and thiamine) [8]. In the 1980s, USA scientists performed nutrition studies (nutritional status and diet) on DS children aged 6 months to 6 years which demonstrated that 80% of those at 6 years were overweight and obese. Dietary intake deficiencies of nutrients were also observed due to an inappropriate diet and a dysfunctional gastro intestinal system that impeded the absorption of nutrients [32]. Similar results were found by *Reading* et al. [35] where, additionally, a link was noted between food allergies with malabsorption and nutrient deficiencies (vitamins and minerals).

The chromosome 21 dysfunction in DS subjects was positively correlated with adverse lipid profiles [2, 5, 30].

Frequently high serum triglycerides but low HDL--cholesterol levels are also observed [10, 23, 27, 33, 37]. Furthermore, in DS subjects, raised leptin concentrations are correlated with high body fat content as well as tissue becoming leptin resistant; a hormone affecting hunger and satiety centres thus impacting on appetite with elevated levels of leptin thereby increasing appetite [7, 9, 20, 38]. A study by *Adelekan* et al. [2] on 36 DS children demonstrated an adverse lipid profile, raised blood leptin levels and a prevalence of overweight and obesity. They further showed an increased likelihood of contracting cardiovascular disease. Many studies on diet and nutritional status indicate excesses or deficiencies along with low physical activity levels associated with certain body dysfunctions and an unwillingness to perform physical activity. The increased risk of overweight and obesity in DS children is linked to a genetic predisposition, high serum cholesterol, hypothyroidism, abnormal diet, social stigma, slower than normal metabolic rate (by 10-15%) and being averse to physical activity [1, 3, 4, 8, 18, 43]. Every 10th person with DS, suffers from depression and anxiety. Such disorders are difficult to diagnose and they occur more often in adults; around 30 years age. Depression significantly affects eating disorders such as making inappropriate food choices, comfort eating, increased or loss of appetite and compulsive eating [31, 36, 44].

These findings demonstrate the need for appropriate modelling of nutritional behaviour in those children with DS, from the earliest ages, so that normal/appropriate/correct eating habits are developed in later life. Such subjects are vulnerable to either imitating or routinely falling into bad habits because of mental disabilities. Normal dietary habits may be learnt by following the parents' example and always making the right choices of foodstuffs [11, 14, 42].

MENTAL RETARDATION AND NUTRITIONAL DETERMINANTS

DS children find it difficult to concentrate, are prone to be confused by environmental factors, have problems with focusing on objects or tasks, possess lowered capacity for spontaneous action as well as emotions and behaviour being out of control, impaired sensory cognition/perception of objects, defective mental processes associated with interpretation, organisation, memory and logical thinking. These intellectual disabilities can be measured by IQ and it is found that in most cases such results are either rather modest (in the 50-70 IQ range) or limited (IQ of 35 – 50). The IQ test assesses the DS child's ability to deduce, think (including being creative) and interpret. It is seen that IQ levels decrease with age coupled with speech impediments, memory loss and a distorted perception [36]. Vitamin and mineral deficiencies occur in DS children, particularly for the B vitamins group (ie. B_1, B_2, B_6, B_{12} and folic acid), which are responsible for intellectual development. These deficiencies in DS children result in intellectual disabilities. Vitamin B_1 deficiency causes weakness, constipation and decreased mobility, whereas B_2 deficiency results in cracked lips and mouth corners, tongue alterations, bleeding gums and conjunctivitis. Vitamin B_6 deficiency gives rise to mental retardation, low physical activity and a lack of concentration. Joint deficiencies of vitamins B_6, B_{12} and folic acid are linked to abnormal blood concentrations of homocysteine in DS children [2, 19, 36, 42, 50].

Zinc, selenium and calcium deficiencies are manifest in DS children [17, 36, 42]. The former significantly affects thyroid metabolism, immunity, ensuring appropriate stature, nucleic acid metabolism, and gene expression and is a component of many enzymes. Zinc deficiency causes abnormal body growth, lowered immunity and thyroid dysregulation (mainly hypothyroidism) [34, 40]. A few studies indicate beneficial effects of zinc supplementation or through adopting a zinc rich diet [6, 25, 46].

A SYDROME OF DOWNS AND *ALTZHEIMER'S* DISEASE

In addition to intellectual disabilities, DS children display rapidly progressing dementia arising from cell-

-damaging oxidative stress and the development of *Alzheimer's* disease. Emergence of the latter appears rather early (at around 20 years) where its development rate is faster than those without genetic defects. One of the principal genes responsible for *Alzheimer's* disease is over-expression of the APP gene on chromosome 21 that codes for the beta amyloid precursor protein resulting in increased production and storage of amyloid; being so responsible for the early-onset aging characteristic of *Alzheimer's* disease [16, 36, 49]. Early onset of *Alzheimer's* disease in DS persons is mainly due to genetic factors and also nutritional ones, where diets rich in fats and straight-chain carbohydrates enhance the accumulation of atheromatous plaques, hypercholesterolemia together with vitamin and mineral deficiencies; there is also a greater reluctance for engaging in physical activity and those exercises designed for normal mental development.

In order to slow down *Alzheimer's* disease, parents or guardians of DS children should take measures for preventing this disease developing at the earliest of years, by ensuring an appropriate diet is followed; ie. one rich in vitamins, especially of the B group as well as antioxidants, (eg. vitamin E), minerals (particularly magnesium), complex carbohydrates, dietary fibre, *omega*-3 fatty acids. Physical and mental activities should also be undertaken [26, 39].

CONCLUSIONS

DS is one of the most common genetic disorders associated with many dysfunction of the body. Early neuro-stimulation and having an appropriate working relationship with tutors may effectively reduce developmental or social-adaptation deficits. Overweight, obesity, vitamin and mineral deficiencies, high total cholesterol, Type II Diabetes can be either eliminated or risk-reduced by adopting an appropriately balanced diet at the earliest of ages together with undergoing nutritional education.

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