ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 01, pp.18389-18393, January, 2018

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

NUTRITIONAL STATUS, COGNITIVE DEVELOPMENT AND PLASMATIC LEVELS OF ZINK AND ALUMINUM IN CHILDREN WITH DOWN SYNDROME

Ana Carla Gomes Rosa, Lourdes Zélia Zanoni, Petr Melnikov and *Valter Aragão do Nascimento

Postgraduation Program in Health and Development in the Middle West Region, Federal University of Mato Grosso do Sul, Brazil, Zip code, 79070900, Campo Grande, MS, Brazil

ARTICLE INFO

Article History:
Received 19th October, 2017
Received in revised form
27th November, 2017
Accepted 29th December, 2017
Published online 31st January, 2018

Key Words:
Down syndrome,
Nutritional status,
Cognitive development,
Zinc, Aluminum.

ABSTRACT

The present study evaluated nutritional status and cognitive development of children and adolescents with Down syndrome. In parallel, plasma concentrations of zinc and aluminum were determined. The research was carried out in Campo Grande, Middle Western Brazil. Thirty individuals from 6 to 16 years old participated in the study. The Human Figure Drawing test III for the assessment of cognitive development was used. The prevalence of overweight and obesity is high, exceeding the rates observed in children with typical development. The psychological evaluation by the DFH III test confirms the delay of the cognitive maturity of those with DS around 50% of the chronological age. Zinc deficiency is present in a significant number of children with DS. The excess of plasmatic aluminum may represent a risk factor for a significant percentage of individuals with DS. Neither zinc nor aluminum in the plasma seems to affect the cognitive maturity of young individuals with DS.

Citation: Ana Carla Gomes Rosa, Lourdes Zélia Zanoni, Petr Melnikov and Valter Aragão do Nascimento, 2018. "Nutritional status, cognitive development and plasmatic levels of zink and aluminum in children with Down syndrome", *International Journal of Development Research*, 8, (01), 18389-18393.

INTRODUCTION

Down syndrome (DS) is a chromosomal disorder with an occurrence estimated between 3.05 and 14 cases per 10,000 live births in the United States and China. In Sweden, most of fetuses with Down syndrome are diagnosed and aborted, but the incidence of live births with Down syndrome kept stable at approximately 0.1%, probably because of the mean age of the Swedish mothers which increased from 26 to 31 years over the last decades. Other countries, such as France, Italy and Denmark, reported decreasing rates of live births with Down syndrome, as low as 0.05%, presumably as a result of more extensive prenatal screening programs (Bergström *et al*., 2017). A prospective study held in the United Kingdom, according to the database created in 1987, found that until July 1st 2014, 2,476 live births had DS, of which 1159 were female and 1317 male, thus showing that Down's syndrome affected more males than the females (Alexander *et al*., 2016). The study of cell culture for fibroblast analysis, carried out in Nagasaki, Japan by Kawakubo *et al*., 2017 showed a larger number of male patients born alive with Down syndrome. Recent studies in Brazil showed a prevalence of population between 6.1 and 13.1 per 10,000 people in about 270,00 people with Down syndrome (1.3 boys to 1.0 girls) (Bertapelli *et al*., 2017; Silva and Miraglia., 2017). In Down syndrome a delay in cognitive capacities occurs in the linguistic development and short-term auditory memory resulting in difficult speech and expressing himself insofar as for the individual understands what is spoken. This alters consequently the development of other cognitive abilities (Deitz *et al.,* 2011; Niccols *et al.,* 2003). Researchers have reported findings such as the emergence of new features of the syndrome that were previously unknown, that is a higher incidence of Alzheimer's disease in people with Down syndrome - about 15% above 40 years and 50-70% after the age of 60. (Weksler *et al.,* 2013) Serrano *et al.,* 2016 identified, for the first time, changes in gene expression occurring in the brain of patients with Down syndrome throughout their lifetime in which the establishment of the cerebral white matter is altered from childhood to adulthood, and that these changes occur due to defects in the development

***Corresponding author:* Valter Aragão do Nascimento,**
Postgraduation Program in Health and Development in the Middle West Region, Federal University of Mato Grosso do Sul, Brazil, Zip code, 79070900, Campo Grande, MS, Brazil.

of a type of brain cell, called oligodendrocyte. This leads to a lower formation of white matter and, consequently, to a slower nerve transmission. Micronutrients play an important role in human metabolism. One of the essential micronutrients of relevant functional importance is zinc due to its effects on the Central Nervous System. It is present in high concentrations in the brain, linked to proteins, as part of their structure and acting in the formation of the neural tube. This mineral intensely participates in the cerebral function, in the synaptic cleft and consequently in the neuronal activity. It is also involved in the memory processing, behavior, cognitive and motor development (Mafra and Cozzolino, 2004; Salgueiro *et al.*, 2000; Singh, 2004; Bhatnagar and Taneja, 2001). Zinc influences brain plasticity, memory and learning processes. The action of this element can be proven already in the gestational period, during the embryogenesis.

The role of zinc in cognitive development has also been described, emphasizing the importance of dietary adequacy in childhood (Singh, 2004). According to the World Health Organization, zinc deficiency is one of the ten major causes of illness in developing countries, being overcome only by iron deficiency (World Health Organization, 2014). Zinc daily dietary intake recommendation (Dietary Reference Intakes) is 11mg/day for men and 8 mg/day for women, but at some stages of life zinc needs are increased, such as during pregnancy, childhood, puberty, and senility (Hambidge *et al.,* 2008). Due to zinc essentiality, the human organism maintains the concentrations of this mineral in a narrow interval, and the plasma level of zinc considered as normal ranges from 0.7 to 1.2 mg/L (Henry, 2008). The role of zinc was especially important in the alterations that occur in DS patients, particularly in their neuroendocrine and immunological systems (Fabris, 1984). The literature is contradictory regarding the concentration of zinc in children with DS, showing either low or normal plasma levels. However, most studies indicate that low levels are prevailing (Barlow, 1981; Björkstén, 1980; Lima *et al.,* 2010). In subjects with DS, the metabolism of aluminum is particularly altered, thus establishing a relation between aluminum brain deposition and Alzheimer's disease (AD) (Riihimaki, 2000). According to Tchounwou *et al*., (2014) it is estimated that the human body contains an average of 35 to 50 mg of aluminum of which approximately 50% are in the lungs and 25% in bone tissue. The concentration acceptable as normal in human plasma is between 7 to 10 µg/L. Aluminum is present in minimal quantities in animal tissue, blood and urine. The highest concentrations are found in the lungs probably due to atmospheric pollution (Tchounwou *et al.,* 2014). In the adult's normal diet, aluminum intake is usually around 3 mg to 10 mg per day, although people on special medication can ingest more than 1,000 mg/day, usually in the form of aluminum hydroxide. In healthy individuals, only 0.3% of ingested aluminum is absorbed by the digestive system (T'sjoen *et al.,* 2005).

The damage caused by aluminum in the brain tissue is mainly due to oxidative stress (Becaria *et al.,* 2006). Among the harmful effects caused by aluminum is the Alzheimer's disease. AD is the most prevalent neurodegenerative disease in the elderly and is characterized by a major impairment of cognitive functions. It is also known that the excess of aluminum in the cerebral tissue alters the calcium metabolism triggering the neuron death (Drago *et al.,* 2008). The study carried out by Moore *et al.*, 1997 highlighted the implication of aluminum in the pathogenesis of both DS and AD, and in both clinical conditions the aluminum accumulates in the same parts of the brain. In these individuals, the transferrin, the protein that carries aluminum present in the plasma, displays a functional defect which favors the accumulation of aluminum in the cerebral tissue. A study in adults with DS showed that intestinal absorption of aluminum is increased in those with DS, resulting in higher plasma concentration (Moore *et al.,* 1997). There are also reports suggesting that, with the increasing age in DS, aluminum concentrations tend to increase in the lungs, liver, kidneys and even brain tissue (Crapper and Deboni, 1978). So far, we have not been able to find in the literature reports on plasma aluminum concentrations in children with DS for the age group of 6 to 16 years. This research is dedicated to the dosage of zinc and aluminum content in children of the previous group, with the purpose of finding possible correlations between metal levels and cognitive development.

MATERIALS AND METHODS

Application of Psychological Testing with Drawing

The psychological evaluation consists of a process that allows obtaining knowledge about the psychic functions of the individual, besides investigating symptoms, permitting a broader understanding of the case served (Nunes *et al*., 2006). The instrument of evaluation should always be representative of the behavior of a sample that can have its data analyzed statistically, based on psychometric characteristics. Thus, it can be considered as a set of items that measures a certain psychological phenomenon (Pasquali, 1999; Anastasi and Urbina, 2000).

The Human Figure Drawing in Cognitive Evaluation

The selection of the Human Figure Drawing (DFHIII) for the evaluation of the child's intellectual development was based on the fact that the human figure is equally familiar to all children, presenting in its essential aspects the smallest possible variability, being a simple task to be performed by very young children, and at the same time complicated enough in their details to assess the ability of a teenager, and finally, be a topic that interests and motivates children, facilitating their involvement in the task as well as their validation already been proven in cognitive assessments for children with Down syndrome (Kolck, 1984; Cox and Maynard, 1998; Pancanaro, 2007).

Casuistry and Methods

It is a prospective, cross-sectional, descriptive and analytical study. This was carried out at the two special education schools in Campo Grande, MS Brazil. The study period lasted from April to July 2014. Regarding ethical aspects, the study was approved by the Ethics Committee for Research on Human Beings, Federal University of Mato Grosso do Sul, number 24695913.6.0000.0021. The Term of Free and Informed Consent was previously read and signed by the person responsible for each participant of the study. Thirty children and adolescents of both sexes, residents in the city of Campo Grande aged 6 to 16 years old with clinical and laboratory diagnosis of Down syndrome were studied. All participants attended regular school. Children with infectious, acute or chronic inflammatory processes, metabolic diseases,

liver or renal insufficiency did not participate in the research. Indigenous and those taking medication containing zinc and/or aluminum, or on indirect supplementation of these minerals also were excluded from the study. According to the methodology established by Cronk graphs of specific growths, in percentile (Mustacchi, 2002) and the nutritional status of the individuals with Down syndrome was evaluated by weight in relation to age (W/A), height in relation to age (H/A) and weight relation to height (W/H). The weight value was obtained using a Filizola scale platform-type scale for adults with graduation of 100g. The individual was positioned only with underwear, with arms outstretched, so that the weight was equally distributed on the surface of the scale, providing greater comfort and lower risk of accidents (Miller, 2007). The height was measured in a vertical stadiometer, which consists of a fixed endometrium on a vertical fixed plane and a portable wooden graded square in millimeters that runs parallel to the vertical plane and forms a right angle. The stadiometer was supported on a flat surface on the ground. When correctly positioned, the portable square was adjusted to the upper cephalic portable with no compression and then the reading was done (Lopes *et al*., 2007; Miller, 2007). The body mass index (BMI) was calculated by the weight / height ratio.

Collection and preparation of samples

All plastic or glass materials used in the study were previously immersed for a minimum of 24 hours in 5% Extran (Merck®) solution, rinsed extensively in running water and again immersed for a period of at least 24 hours in 10% nitric acid solution (Merck®), for decontamination of any metal residue. Then they were washed with ultrapure Milli-Q-water (Millipore, Bedford, USA) and in oven dried at 70 °C. Blood samples for laboratory analysis were collected in the morning with individuals who have fasted. Each sample was transferred to a vacuum polypropylene tube, suitable for trace element collection (BD Vacutainer Systems) ® and centrifuged for 15 minutes at 3,000 RPM. Plasma was placed in polypropylene Eppendorf tubes and immediately frozen at -18 °C.

Inductively Coupled Argon Plasma Optical Emission Spectroscopy

For trace elements determination, the samples were defrosted and 0.5 ml of each one was diluted in a volume of 4.5 ml of ultra-pure Milli-Q type water with 1% nitric acid (HNO_3), to 0.01% Triton X® (surfactant), reaching a final volume of 5 mL. The plasma, zinc and aluminum readings were performed using an Inductively Coupled Argon Plasma Optical Emission Spectrometer (ICP-OES) of the Thermo® brand. ICP-OES is a sequential/simultaneous analysis technique that is based on observations of radiation emissions of the constituents of the sample in coupled argon plasma. The wavelengths for reading of zinc and aluminum were 213.86 nm and 196.09 nm, respectively.

Psychological evaluation

The drawing of the Human Figure III, was performed by all participants for psychological evaluation. The analysis of the results was corrected based on the Wechsler system of evaluation of the DFH III with Brazilian standardization. Each participant received a pencil and a self-test sheet and was asked to draw a man and a woman, not necessarily in that order. An approximate time of 30 minutes was given for each participant to complete the two drawings (Wechsler, 2003). The Human Figure test is specific for application in children ranging from 5 to 12 years old. It is validated, according to the parameters of Resolution 002/2003 of the Brazilian Federal Council of Psychology. Its interpretation was carried out according to the child's age. It was based on the evaluation of 58 evolutionary items for the male figure and 53 evolutionary items for the female figure that are scored as absent or present. A global score is based on the sum of items classified as expected, common, unusual, and exceptional, according to the child's age (Bandeira and Hutz, 2006). The correction system aiming to compare the results of each child with a group of children of the same age was applied. The final interpretation of the results allowed classifying the cognitive development of the studied child, that is, the level of conceptual maturity in relation to the children of the same age range.

DFH III test and FIC score

The comparison between the sexes in relation to the age, height, weight, zinc and aluminum plasma content, percentile in the DFH III test and score confidence interval factor (FIC) was performed by means of the Mann-Whitney test, since the data samples did not pass the Kolmogorov-Smirnov normality test. The evaluation of the linear correlation between the zinc plasma or aluminum concentrations, with the variables age, height, body weight, percentile in the DFH III test and FIC score was performed by means of the Spearman linear correlation test. The rest of the variables evaluated in this study were presented either in the form of descriptive statistics or in the form of tables and graphs. Statistical analysis was performed using the statistical program SPSS, version 22.0, considering a level of significance of 5%, namely $p \leq 0.05$ (Enumo, 2010).

RESULTS AND DISCUSSION

In this research we were able to confirm that DS occurs predominantly in males, remaining the male/female ratio in 1.5: 1, similarly to the previously published data, from Mexico and Brazil, in particular. It was shown that 13% (n = 11) of the children with DS showed prevalence of overweight and 50% (n = 15) the prevalence of obesity, in line with research conducted in Australia. (Krause *et al*., 2016) in a cross-sectional survey of medical records of 261 intellectually disabled adolescents attending special education facilities in Southeast Queenslland. Data were collected on age, gender, weight, height, specific diagnoses of syndrome, problematic behaviors, mobility, use of psychotropic or epileptic medication and possible financial difficulties. Overall (22.5%) of adolescents were obese and (23.8%) were overweight, meaning a sharp increase over Australian standards. Adolescents with DS were more likely to be obese than other participants (odds ratio = 3.21, 95% CI: 1.41-7.30). In this work no association was found with other risk factors examined. The prevalence of obesity and overweight increased in comparison with Australian adolescents in general. The only significant risk factor was the presence of Down syndrome. These findings reinforce the need for a health policy and a practical response to obesity that includes individuals with intellectual disabilities. It was observed (Nascimento, 2016) in a study composed of 41 children and adolescents of both sexes, aged between 9 and 19 years, including 26 DS children that in the DS group the overweight and obesity rate constituted 50%. Caloric intake in both groups was in

accordance with the daily recommendations, but protein intake was higher than recommended for both groups and exceeded the indexes observed in children with typical development. Zinc deficiency in this study was present in a significant number of individuals with DS. The mean plasma zinc concentration among female participants was 93.11 ± 6.14 µg/dL, while in the male group it was 101.93 ± 6.83 µg/dL. As for the analysis of individual cases, 6.7% (n = 2) of the subjects presented plasma zinc concentration below 70µg/dL. When considering the lower limit of 80 µg/dL, the number of individuals increases to 9, representing 30% of the studied group. This is in accordance with researches conducted in Brazil and the United Kingdom, showing (Yani *et al.,* 2016) that almost two billion humans in the world suffer from zinc deficiency. On the other hand, a study conducted by Smith *et al.* (2017) in São Paulo, revealed that in 13 children with Down's syndrome the consumption of micronutrients as calcium, iron, fiber and zinc were below that those recommended by DRI in most participants. According to the latest publication (Mirza, 2017), in a study carried out on brain tissue from 12 adult participants with familial Alzheimer's disease it was confirmed that, in fact, the aluminum contents were high. There is no evidence in the literature of studies neither of plasma nor tissue levels of aluminum in children and young people with DS within the age group of 6 to 16 years. At the same time, the results of the present study suggest that in the above group excess plasma aluminum may represent a risk factor for a significant percentage of individuals with DS.
The psychological evaluation by the DFH III test confirms the delay of the cognitive maturity of those with DS around 50% of the chronological age. Actually, the above test verifies the degree of conceptual maturity which is one of the aspects of intellectual functioning. There were no statistical correlations in this study of plasma zinc and aluminum concentrations with the cognitive development of individuals with DS.

Conclusion

- The present study evaluated nutritional status and cognitive development of children and adolescents with Down syndrome within the age group of 6 to 16 years.
- The prevalence of overweight and obesity is high, exceeding the rates observed in children with typical development.
- The psychological evaluation by the DFH III test confirms the delay of the cognitive maturity of those with Down syndrome around 50% of the chronological age.
- Zinc deficiency is present in a significant number of children with Down syndrome.
- The excess in plasmatic aluminum children with Down syndrome is confirmed.
- Neither zinc nor aluminum in the plasma seems to affect the cognitive maturity of young individuals with Down syndrome.

REFERENCES

Alexander M, Ding Y, Foskett N, Petri H, Wandel C, Khwaja O. 2016. Population prevalence of Down's syndrome in the United Kingdom. *J Intellect Res*., 60:874–878.

Anastasi A. and Urbina S. 2000. Testagem psicológica. 7th ed. Porto Alegre: Artes Médicas.

Bandeira DR. and Hutz CS. 2006. Desenho da figura humana. In: Cunha JA. Psicodiagnóstico. 5th ed. Porto Alegre: Artes Médicas.

Barlow PJ. 1981. Hair trace metal levels in Down's syndrome patients. *J Ment Defic Res*., 25:161-168.

Becaria A, Lahiri DK, Bondy SC, Chen D, Hamadeh A, Taylor R. and Campbell A. 2006. Aluminum and copper in drinking water enhance inflammatory or oxidative events specifically in the brain. *J Neuroimmunol*., 76:16-23.

Bergström S, Carr H, Petersson G, Stephansson O, Bonamy. AK, Dahlström A, Halvorsen CP, Johansson S. 2016. Trends in congenital heart defects in infants with Down Syndrome. *Pediatrics,* 138:1-11.

Bertapelli F, Machado MR, Roso RV. and Guerra-Júnior G. 2017. Body mass index reference charts for the individuals with Down syndrome aged 2-18 years. *J Pediatr*., 93:94-99.

Bhatnagar S. and Taneja S. 2001. Zinc and cognitive development. *Br J Nutr*., 85:139-145

Björkstén B. 1980. Zinc and immune function in Down's Syndrome. *Acta Paediatr Scand.,* 69:183-187.

Cox MV. and Maynard S. 1998. The human figure drawings of children with Down syndrome. *Br J Develop Psyc*., 16:133-137.

Crapper DR. and Deboni U. 1978. Brain aging and Alzheimer's disease. *Can Psychiatr.,* 23:229-233.

Deitz SL, Blazek JD, Solzak JP. and Roper RJ. 2011. Down Syndrome: A complex and interactive genetic disorder. Indiana University-Purdue University Indianapolis. United States of America. Available in: https://cdn.intechopen. com/pdfs-wm/18439.pdf Accessed 16 November 2017.

Drago D, Cavaliere A, Mascetra N, Ciavardelli D, Di IC, Zatta P. and Sensi SL. 2008. Aluminum modulates effects of beta amyloid (1-42) on neuronal calcium homeostasis and mitochondria functioning and is altered in a triple transgenic mouse model of Alzheimer's disease. *Rejuvenation Res*., 11:861-871.

Eggermann T. and Schwanitz G. 2011. Genetics of Down Syndrome. Available in: http://www.intechopen.com/ books/genetics-and-etiology-of-down-syndrome/genetics-of-down-syndrome. Accessed 16 November2016

Enumo, SRF. 2010. Avaliação assistida para crianças com necessidades educacionais especiais: um recurso auxiliar na inclusão escolar. *Rev Bras. Educ. Espec*., 11:335-354.

Hambidge MK, Miller, LV. and Westcott JE. 2008. Dietary Reference Intakes for zinc may require adjustment for phytate intake based upon model predictions. *J. Nutr.,* 138: 2363-2366.

Henry JB. 2008. Diagnósticos clínicos e tratamento por métodos laboratoriais. 20th ed. São Paulo: Manole**.**

Kawakubo T, Mori R, Shirotani K, Iwata N. and Asai M. 2017. Neprilysinis suppressed by dual-specificity tyrosine-phosphorylation regulated kinase 1A (DYRK1A) in Down-Syndrome-derived fibroblasts. *Biol. Pharm. Bull*., 40:327-333.

Kolck VL. 1984. Testes projetivos gráficos no diagnóstico psicológico. 8th ed. São Paulo: Editora Pedagógica e Universitária.

Krause AS, Wareb R. Mcpherson L, Lennox N. and Callaghan MO. 2016. Obesity in adolescents with intellectual disability: Prevalence and associated characteristics. *Obes Res Clin Pract*., 10:520-530.

Lima AS, Cardoso BR. and Cozzolino SF. 2010. Nutritional status of zinc in children with Down Syndrome. *Biol Trace Elem Res.,* 133:20-28.

Lopes LA, Patiin RV, Weffort VRS, Filho SD. and Palma D. 2007. Avaliação do estado nutricional. In: Lopes FA, Júnior DC(Org). Tratado de Pediatria. 3th ed. São Paulo: Manole.

Mafra D. and Cozzolino SMF. 2004. Importância do zinco na nutrição humana. *Rev Nutr.,* 1:79-87.

Miller R. 2007. O exame morfológico da criança. In: Lopes FA, Júnior DC(Org).Tratado de Pediatria. 4th ed. São Paulo: Manole.

Mirza A, King A, Troakes C. and Exley C. 2017. Aluminium in brain tissue in familial Alzheimer's disease. *J Trace Elem Med Biol.,* 40:30-36.

Moore PB, Edwardson JA, Ferrier IN, Taylor GA, Lett D, Tyrer SP, Day JP, King SJ. and Lilley JS. 1997. Gastrointestinal absorption of aluminum is increased in Down's Syndrome. *Biol Psychiatry.,* 41:88-92,

Mustacchi, Z. 2002. Curvas padrão pondero estatural de portadores de Síndrome de Down procedentes da região urbana da cidade de São Paulo, Thesis in Pharmacy, University of São Paulo/SP.

Nascimento EF. Análise da composição corporal por meio de DEXA em crianças e adolescentes com síndrome de Down. 2016. Thesis in Physical Education and Health, Catholic University of Brasília, Brasilia/DF.

Niccols A, Atkinson L. and Pepler D. 2003. Mastery motivation in young children with Down's Syndrome: relations with cognitive and adaptive competence. *J Intelect Disabi Res.,* 47:121-133.

Nunes MLT, Silva RBF, Deakin EK, Dian SV. and Campezatto PVM. 2006. Avaliação psicológica e a indicação de psicoterapia psicanalítica para crianças. In: Werlang BG, Oliveira MS. Temas em psicologia clínica. 5th ed. São Paulo: Casa do Psicólogo.

Pancanaro SV. 2007. Avaliação de habilidades cognitivas e viso-motoras em pessoas com Síndrome de Down. Dissertation, Master in Psychology-Universidade São Francisco / US, São Paulo-SP.

Riihimaki V, Hanninen H, Akila R, Kovala T. and Kuosma E. 2000. Body burden of aluminium in relation to central nervous system function among metal inert-gas welders. *Scand J Work Environ Health*, 26:118-130.

Pasquali L. 1999. Instrumentos psicológicos: Manual prático de elaboração. 8th ed.Brasília: LabPAM& IBAPP.

Salgueiro MJ, Bioch MZ. and Lysionek A. 2000. Zinc as an essential micronutrient: a review. *Nutr Res.,* 20:737-755.

Serrano JLO, Kang HJ, Tyler WA, Golden JA, Haydar TF. Sestan N. 2016. Down Syndrome developmental brain transcriptome reveals defective oligodendrocyte differentiation and myelination. *Neuron.,* 89:1208–1222.

Silva FG and Miraglia F. 2017. Análise do consumo alimentar em indivíduos com síndrome de Down da região metropolitana de Porto Alegre. *Cinergis*., 18:93-98.

Singh M. 2004. Role of micronutrients for physical growth and mental development. *Ind J Ped*., 1:59-62.

Smith ARSS, Santos SS, Silva RC and Alvarenga ML. 2017. Estado nutricional de crianças e adolescentes com síndrome de Down praticantes de judô. *Rev. Bras de Nutr Esport.,* 11: 410-419.

Tchounwou PB, Yedjou CG, Patlolla AK. and Sutton DJ. 2014. Heavy Metals Toxicity and the Environment. Available in: https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC4144270/pdf/nihms414261.pdf Accessed 27 November 2017

T'sjoen GG, Beguin Y, Feyen E, Rubens R, Kaufman JM. and Gooren L. 2005. Influence of exogenous oestrogen or (anti-) androgen administration on soluble transferrin receptor in human plasma. *J Endocrinol*. 186:61-67.

Wechsler SM. 2003. DFH-III - O desenho da figura humana: Avaliação do desenvolvimento de crianças brasileiras. 3th ed. Campinas: IDB Impressão Digital do Brasil/ Laboratório de Avaliação e Medidas Psicológicas-LAMP

Weksler ME, Szabo P, Relkin NR, Reidenberg MM, Weksler BB. and Antonia MW. 2013. Alzheimer's disease and Down's syndrome: Treating two paths to dementia. *Coppus.,* 12:670-673.

World Health Organization - WHO - 2014 - Global Database on Child Growth and Malnutrition. Available in: http:// www.who.int/gdgm/p-child_pdf/. Accessed Jun 12 2017.

Yani RWE, Mallongi A, Andarini S, Prijatmoko D. and Ida RD. 2016. The effect of zinc saliva on the toddlers' nutritional status. Clinical article *J Int Dent Med Res.,* 9:29-32.

****