Journal of Advances in Medicine and Medical Research

26(7): 1-14, 2018; Article no.JAMMR.41138
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

An "Abundance" Phenotype Hypothesis for Autism

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/41138
Editor(s):
(1) Mohamed Essa, Department of Food Science and Nutrition, Sultan Qaboos University, Oman.
Reviewers:
(1) Dario Siniscalco, University of Campania, Italy.
(2) Ibrahim El-Zraigat, University of Jordan, Jordan.
(3) Monday Igwe, Ebonyi State University, Nigeria.
Complete Peer review History: http://www.sciencedomain.org/review-history/24758

Review Article

Received 6th March 2018
Accepted 16th May 2018
Published 23rd May 2018

ABSTRACT

Autism spectrum disorder (ASD) is significantly increased in recent decades, all over the world. The enlargement of the disorder's diagnostic criteria and the increased accessibility of diagnostic and treatment services, are not the only factors that could explain the phenomenon.

Literature review was made in order to formulate a possible explanation for autism epidemics today. So, different phenotypic characteristics of autism (such as macrocephaly, megalosomy, obesity), laboratory findings (such as increased BDNF, IGF-1, IGF-2, IGFBP-3, GHBP, testosterone and oxytocin), and some autism risk factors (such as maternal metabolic conditions, prenatal and postnatal nutritional supplements, infant milk formula and breastfeeding) are discussed from an ecological and evolutionary neuropathology aspect and it is proposed that autism is the result of increased activation of growth pathways, especially at neural tissue and it may represents an adaptive response to modern urban "environmental abundance".

It is thus proposed that autism is the result of epigenetic disruption in brain development caused by gestational exposure to these conditions (which interfere with neurogenesis).

So, it is hypothesized that autism is the physiological and ecological cost that is paid for the enhanced growth rate activation, especially in neural tissue, due to increased resource and energy availability during prenatal and postnatal period of increased plasticity (excess numbers of neurons are produced but they are also liable to impairment).

So, an "abundance" phenotype hypothesis for autism may emerge, a holistic approach of childbirth

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would be possible and well organized preventive programs (about parental health and nutrition before conception, nutrition of pregnant woman and child, optimal breastfeeding, rational use of nutritional supplements, etc) could be carried out.

Keywords: Autism spectrum disorder; abundance phenotype.

1. INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by intellectual and communicative deficits, obsessive compulsions/interests, an extremely rigid or narrow way of thinking, and repetitive or ritualistic behavior patterns [1].

The prevalence of ASD is dramatically increased in recent decades across the world. The increased awareness as well as the broadening of the definition of symptoms to meet the criteria for a diagnosis, which has caused increasing numbers of individuals to receive an ASD diagnosis [2], is not the only explanation.

These data confirm that ASD prevalence is a continuing urgent public health concern and that efforts are needed to identify potential risk factors likely to be contributing to this astounding increase, especially in a short period.

2. AUTISM AS INCREASED GROWTH – SIGNALING PATHWAY ACTIVATION

There are many evidences that an overgrowth pattern runs the autistic disorder as a whole, from prenatal period until adult life of the autistic individuals.

2.1 Highly Proliferative Placentation

The human placenta mediates interactions between mother and fetus throughout gestation and provides a historical record of maternal physiologic influences on the fetus. The placentas from women whose fetuses are at elevated risk for autism are markedly different from control placentas. These differences are manifested histologically as trophoblast inclusions [3]. Trophoblast inclusions are the result of abnormal infoldings of the trophoblast bilayer and represent an abnormal balance of placental cytotrophoblast proliferation and differentiation. Trophoblast inclusions were more frequent among placentas from women whose fetuses were at elevated risk for autism than control placentas, suggesting that increased cellular and tissue proliferation during fetal life might reflect augmented generalized growth processes that could result in neurodevelopmental changes [4].

2.2 Macrocephaly in Autism

Researchers have demonstrated that children diagnosed with ASD show an abnormal acceleration of head growth [5-8] and that early abnormal brain overgrowth occurs at the time of the first detectable behavioral and clinical signs of autism [9-10]. Now macrocephaly is considered as an autism endophenotype and abnormal accelerated rate of head growth may serve as an early warning signal of risk for autism. So, it is supported the inclusion of this characteristic in multibiomarker diagnostic panels for clinical use [11].

Macrocephaly possibly suggests neurons overdevelopment, consequent to cell cycle dysregulation and/or failure of naturally occuring apoptosis (impaired prunning) [5,6] and abnormal neural connectivity [12].

Also, researchers have found that head size is higher in low functioning people with ASD compared to high functioning ASD individuals [11] and that greater symptom severity is correlated with greater deviation from normal brain maturation [13].

The association of increased trophoblast inclusions in the placentas of ASD and at-risk newborns suggests a possible common abnormality that is manifested by increased cellular growth and tissue folding in both the placentas and brains of these children [4].

2.3 Increased Levels of Brain-Derived Neurotrophic Factor (BDNF) and Other Neurotrophic Factors in Autism

Neurotrophic factors as survival-promoting molecules are essential regulators of neuronal maturation including synaptic synthesis. Among those, brain-derived neurotrophic factor (BDNF) plays a vital role in the survival, growth,

development, differentiation maintenance, and function and plasticity of neurons throughout the brain spinal cord [14]. Research findings suggested a critical role played by BDNF in the development of autism including increased concentrations of BDNF in both blood and brain tissue in children with autism and identification of different forms of BDNF in families of autistic individuals [15-17]. Increased levels of BDNF and other neurtrophic-like factors in autism suggest that enhanced anabolic activity in central nervous system mediates this brain overgrowth effect [18,19]. Children with severe autism and aggression express higher levels of these neurotrophic factors and these findings do not extend to patients to mild-to-moderate autism, providing a biochemical correlate of phenotypic severity. Higher BDNF levels could be considered an independent diagnostic marker of ASD [19,20].

2.4 Increased Levels of Growth Hormones, Megalosomy and Obesity in Autism

Children with ASD are also significantly longer and heavier at the first year of life. Accelerated head circumference reflects a generalized process affecting other morphological features, including weight and height [21] and it is assumed that autism possibly is due to a dysregulation of growth factors in general, rather than to a disregulation of neural growth in the brain [22]. Children with ASD are also at risk for overweight and obesity later in their life [23-27], regardless of psychotropic medications prescribed [28]. Also, the prevalence of unhealthy weight is significantly greater among children with ASD compared with the general population, with differences present as early as ages 2 to 5 years [26]. Because obesity is more prevalent among older children in the general population, these findings raise the question of whether there are different trajectories of weight gain among children with ASDs, possibly beginning in early childhood (or even prenatal).

It is important that the presence of a larger body at birth and postnatal overgrowth was associated independently with poorer social, verbal, and nonverbal skills at 4 years. This means that early generalized overgrowth for both neural and non-neural tissue development during prenatal and early postnatal periods may constitute a biomarker for identifying toddlers with ASD at risk for less-optimal outcomes [29].

On the other hand, a study demonstrated that tall stature may be a phenotypic “biomarker” of susceptibility to EEG abnormalities or late epilepsy in ASDs and, when concurring with macrocephaly, predisposes to early onset seizures. Growth pattern might act as an endophenotypic marker in autism-epilepsy comorbidity [30].

Also, children with autism have often significantly higher levels of many growth-related hormones, such as IGF-1, IGF-2, IGFBP-3 and GHBP. These findings may explain the significantly larger head circumference and higher weights and BMIs seen in these subjects [31-33]. On the other hand, IGF-1 has crucial role to play in the development, growth and maturation of the CNS and its synapses [34,35]. Because IGF-1 levels are modifiable through diet and other environmental exposures, this may be one pathway through which the childhood environment may influence neurodevelopment [36].

2.5 Increased Testosterone and Autism

Autism spectrum disorder affects females less frequently than males. In particular, subjects diagnosed with an ASD have a male: female ratio of 4:1 and among subjects diagnosed with Asperger syndrome the male: female ratio is as high as 9:1 [37,38]. Several sex-differential genetic and hormonal factors (especially testosterone, both fetal and later life level) may contribute [39,40]. Recent studies, also, support the hypothesis that autism is associated with an increased rate of testosterone-related medical conditions [41]. All these data strengthen the aspect that an anabolic state predominates in autism. At this point, it is very important to mention that oxytocin levels are decreased in autism [42]. Oxytocin exhibits opposite effects from testosterone on diverse aspects of cognition and behaviour [43]. In particular, oxytocin increases the salience of social stimuli and promotes parental nurturing and social bonds [44]. Numerous clinical trials of oxytocin in ASD therapy are ongoing today [45-51].

2.6 Autism and Cancer

Emerging data suggest that individuals with ASD might have an increased risk for cancer for a number of reasons [52-54]. Similarly, copy number variants identified in children with autism are frequently associated with cancer predisposition genes [55].

DiCicco-Bloom and colleagues suggest that growth factor regulation of neurogenesis and changes in the balance between promitogenic and antimitogenic signals that control neural proliferation may be crucially important in autism [56].

But, cancer is a condition where cells proliferate without control, or, in other words, organism at this situation expands until detrimental results. Similarly, the overgrowth / overdevelopment of organism in autism (increased neurogenesis, accelerated brain growth and growth enhancement in general) results in reduced performance: autistic behavior may emerge.

According to this, it is possible that a pattern of overgrowth/overdevelopment rules both the autism and the cancer, as general conditions.

3. "ABUNDANCE" IN PRENATAL ENVIRONMENT AND AUTISM

3.1 Parental Nutrition and Health

Many studies have been shown that *maternal* metabolic conditions during pregnancy such as *diabetes* (both pregestational and gestational) and *obesity* may be broadly associated with neurodevelopmental problems in children, included ASDs [57-63]. In particular, evidence from both epidemiological studies and animal models indicates that maternal diet (especially *high fat diet consumption*) and metabolic status play a critical role in programming the neural circuitry that regulates behavior, resulting in long-term consequences for offspring behavior. The mechanisms by which maternal diet and metabolic profile shape the perinatal environment remain largely unknown, but recent research has found that increases in inflammatory cytokines, nutrients (glucose and fatty acids), and hormones (insulin, leptin and sex hormones) produced by maternal adipose tissue, affect the environment of the developing offspring via serotonergic system impairment [64, 65]. It is interesting that the risk of offspring ASD is associated with elevated pre-pregnancy body mass index (BMI), with excess maternal gestational weight gain [66-68] and with *paternal* BMI at age 18 [67] –these factors may represent "abundance" in-before conception-and prenatal environment.

3.2 Increased Prenatal Steroidogenic Activity and Autism

It has been already mentioned that elevated fetal testosterone has been proposed to contribute to the development of ASD [40]. Moreover, examination of amniotic fluid samples from children with a clinical diagnosis of ASD and healthy controls have showed elevations among ASD cases in levels of all hormones along the Δ4 sex-steroid biosynthetic pathway, including progesterone, 17a-hydroxy-progesterone, androstenedione, testosterone and cortisol [69]. Moreover, maternal plycystic ovary syndrome (PCOS), a condition associated with excess androgens, increased the odds of ASD in the offspring by 59%, after adjument for confounders. The odds of offspring ASD were further increased among mothers with both PCOS and obesity, a condition common to PCOS that is related to more severe hyperandrogenemia [70]. Also, maternal hirsutism, which is a condition characterized by hyperandrogenism, is associated with child ASD, further strengthening the hypothesis that androgen may be involved in the etiology of ASD [71].

But, hyperandrogenemia is an anabolic state and a sign of "abundance" in prenatal milieu.

3.3 Maternal Folic Acid Intake and Risk of Autism

Today health authorities recommend that all women who plan to become pregnant should take a daily dose of 400 mcg of folic acid and appropriate dietary folic intake from before conception to the third month of pregnancy to reduce the risk of neural tube defects, while not exceeding the tolerable upper intake level of 1000 mcg/day [72].

This nearly universal recommendation, the easy availability of folic acid in over-the-counter prenatal vitamins and the fortified foods may result in population-wide fetal overexposure to folic acid. Significant proportion of pregnant women (10-30%) use high dosages of folic acid (>1000 mcg/day), not including the supplementation they are ingesting, if they eat cereal, bread, or pasta and, moreover, the use of these high dosages of folic acid is unnecessarily maintained after the third month of pregnancy [73-74].

Folic acid is essential for cell division and protein synthesis. When folic acid is too little, these processes are obstructed, especially during time windows such as pregnancy, where folic acid requirement is markedly increased to cove the needs of embryonic and fetal growth and development. Tissues that growth fast (e.g neural) are more susceptible to negative results (neural tube defects, such as spinal bifida, are associated with folic acid deficiency).

If folic acid deficiency causes nervous tissue damage, then it seems reasonable that excess folic acid may results in nervous tissue damage also, associated with autism, in particular. According to the above-mentioned data, when there is excess folic acid, cell division (especially in neural tissue) may be more vigorous. This could be a possible explanation for rapidly increased brain cell numbers (megalocephaly) and cortical thickness in autism. Moreover, there is recent evidence that folic acid leads to increased methylation of the maternally imprinted insulin-like growth factor 2 (IGF2) gene, possibly due to a relative intrauterine silencing of IGF2 [75].

On the other hand, it has been already proposed that excess folic acid supplementation may be a risk factor for autism [76-79], and reports have drawn attention to the possible adverse effects of using high doses of folic acid in general [80-83]. These findings emphasize the need to identify both lower and upper limits for maternal folic acid status during pregnancy in association with fetal growth and long-term health outcomes.

In any case, fetal exposure to high doses of folic acid today represents an “abundant” prenatal environment (in the sense of increased resources availability) that may results in emergence of autistic disorder.

Modern urban life style, obesity, diabetes, high fat diet consumption and so on, may be significant epigenetic factors [84] that create an “abundant” environment for the offspring. But, “more is not always better” and autistic phenotype may emerge.

4. “ABUNDANCE” IN POSTNATAL ENVIRONMENT AND AUTISM

It seems that the “over-supply” environment predominates not only over the prenatal, but the postnatal period also.

4.1 Infant Formula and Autism

Several studies have shown that breast-feeding has a protective effect against the risk of ASD [85,86] and hypotheses have been formulated for explanation of this phenomenon [86] and for the infant formula’s role in increased incidence of autism today [87]. Suboptimal breast-feeding practices are widespread. Worldwide, it is estimated that only 34,8% of infants are exclusively breast-fed for the first 6 mo of life, and most receive nutritionally inadequate and unsafe complementary foods too soon [88].

Majorities of formula in the world are cow’s milk based. The molecular weight of the cow’s milk is much higher than that of human breast milk. Also, protein concentration in cow’s milk formula remains higher (although poorer in quality) in comparison with breast milk, even though formula makers have reduced the amount of whey protein in it. On the other hand, formula makers have fortified new substances (another aspect of “enriched environment”) in the process of formula making whenever they found previous unknown substances in the breast milk, for the past several decades.

Additionally, it is known that feeding with formula milk leads to a greater rate of growth [89]. The formula-fed infants are generally bigger and heavier than that of breast-fed infants. When cow’s milk formula was fed to human baby, they grow faster and bigger, because cows grow faster than human.

Finally, the use of contemporary calorie and protein-enriched formula milk is increased today, because of the viability of preterm and/or low birth weight infants during last decades. Moreover, prematurity has already been identified as independent risk factor for ASD, as several studies have reported an increased prevalence of ASD in preterm populations [90].

According to above-mentioned data, formula-fed infants are exposed to an environment of abundance (artificial, quantitative, not qualitative abundance) early in postnatal life. This may result in enhanced activation of growth pathways, which runs the autistic disorder totally. But, this is a period that massive neurogenesis takes place. So, neural tissue damage may occur.

4.2 Excess Multivitamin Feeding in Early Infancy

It is assumed that excess multivitamin feeding in early infancy (another aspect of the enriched environment) may be a potential risk factor for autism. In particular, autism, according to literature data, is often associated with altered levels of monoamines (serotonin and catecholamines), especially elevated serotonin levels. Monoamine neurotransmitters are enzymatically degraded/inactivated by three mechanisms: oxidative deamination, methylation and sulfation. Excess multivitamin feeding in early infancy, which has become very popular over the past few decades, maybe a potential risk factor for disturbed monoamine metabolism and contribute to increased autism prevalence nowadays [91]. Pediatric vitamins fortified with folic acid and food fortification with vitamins and other substances could contribute to this direction.

4.3 Autism and Socioeconomic Status

It seems that autism prevalence is higher in wealthy populations [92-96]. It is assumed that the higher educational level in these populations results in better accessibility of diagnostic and treatment services. However, no one can rule out other etiological factors of the phenomenon.

5. EARLY RAPID GROWTH AND FUNCTION ARE OFTEN ASSOCIATED WITH POOR OUTCOME AND REDUCED PERFORMANCE

There are several evidences that increased growth, especially early in life, is associated with pathogenesis and a reduction in tissue function.

Consequently, autism could be an example of ecological imbalance, where the overgrowth and overdevelopment pattern results in exhaustion of system regulatory feedback mechanisms and reduced system performance (behavioral symptoms emerge).

5.1 Links of Growth Rate to Lifespan and Healthspan

Several reports indicate that rapid growth early in life is associated with impaired later performance and reduced longevity [97,98].

It is assumed that the greater the investment in growth, the lower the investment in prevention or repair of molecular damage. Rapidly grown structures (i.e. neural tissue) may also be more prone to developmental errors or weaknesses, such that the fast-growing animal is sacrificing “quality” for “speed”. According to this pattern, excess number of neurons is produced in autism, but they undergo in neurodegeneration and reduced tissue performance and function.

Similarly, growth hormones (which it has been found elevated in ASD) are anabolic hormones that increase cellular metabolism and enhance the function of numerous tissues. Besides, it has been shown that the growth hormones-induced increase in metabolic activity is at the expense of increased oxidative damage and risk of pathology and results in increased glucose use and increased oxygen consumption (increased energy expenditure). These effects lead to detrimental consequences, including pathogenesis and a reduction in tissue function [99]. Animal models with reduced GH and/or IFG-1 signalling have been shown to have an extended lifespan as compared to control siblings [100] and healthspan and longevity can be extended by suppression of growth hormone signalling [101]. Finally, it has been shown that any factor preventing an excess of energy consumed and hyperfunction (understood as unnecessary or even adverse syntheses of cell components) leads to increased lifespan, both evolutionary and an individual lifetime scale [102].

5.2 Gh/Igf-1 Axis and Cognitive Function

Experimental data indicate that growth hormones affect mental function (especially memory) unfavourably. In particular, ames dwarf and GHR-/-mice appear to have an apparent delay in mental ageing and improvement in some measures of cognitive function [103].

5.3 Enhanced Growth is Associated with Acceleration of Telomere Loss

Telomeres are DNA structures that protect a chromosome’s end from deterioration, maintaining genomic stability [104]. Telomeres are somewhat shortened every time a cell replicates its DNA before division, for example during growth. Rapid growth has also been correlated with more fast rates of telomere abrasion, possibly due to rates of oxidative damage [105]. Studies on a broad range of

species suggest that telomere length may serve as a fitness indicator, correlating with an individual's longevity and/or reproductive success [106-108].

On the other hand, shorter telomere length has been associated with psychiatric disorders [109], attention-deficit/hyperactivity disorder (ADHD) [110] and autism [111-112]. It is of great importance to be investigated of shorter telomere in autism is correlated with the "over-growth" pattern of the disorder.

Additionally, it is known that there is an association between immune function and telomere attrition. A strong immune system requires sufficiently long telomeres, as an effective immune response relies on the ability of naïve lymphocytes to undergo massive cell divisions [113,114]. The most prevailing opinion is that autism is a neuro-immune disorder [115, 116]. So, there is one more correlation between fast growth, autism, immune system and telomere attrition.

6. AUTISM AND SCHIZOPHRENIA: ABUNDANCE AND DEPRIVATION

Schizophrenia is one more neuropathological situation of human cognition and behaviour that involves altered development and function of the social brain.

It has been already shown that autism and schizophrenia exhibit diametric patterns as regard to behavioural characteristics related to social brain development [117-119].

On the other hand, many phenotypic traits, demographic characteristics and risk factors are diametrically opposite in schizophrenia versus autism. Schizophrenia is correlated to intrauterine growth restriction, placental undergrowth, low maternal body mass index, low birth weight [120-123], small brain size [124], low levels of BDNF and other growth factors (IGF-1, neuregulin, insulin, epidermal growth factor, neurotrophic growth factors etc) [125-127], slow maturation and thinness during childhood [128,129]. Additionally, schizophrenia is associated with low socioeconomic status [130] and cancer risk is low at these patients [131-133].

Moreover, epidemiological studies have identified a strong correlation between schizophrenia and prenatal exposure to famine [134-135], and animal models of prenatal malnutrition display structural and functional brain abnormalities implicated in schizophrenia [136]. It is highly probable that offspring born to a mother that is malnourished will encounter a habitat marked by nutritional scarcity [137].

According to above-mentioned data, it is clear that schizophrenia involves a general pattern of undergrowth and deprivation (versus dysregulated overdevelopment which runs the autistic disorder in general).

7. AN "ABUNDANCE" PHENOTYPE HYPOTHESIS FOR AUTISM

If autism and schizophrenia are diametrically opposite diseases and if schizophrenia is associated etiologically with an environment of deprivation, thriftiness and undergrowth, it is reasonable for a question to arise: is the overgrowth pattern that runs through all over the autistic disorder associated with an environment of abundance and oversupply?

It is proposed that factors such as maternal obesity, diabetes, high fat diet consumption etc constitute environmental abundance before conception, prenatally and postnatally. Consequently, enhanced activation of growth pathways may be happening. This is consistent with the big set of growth-related phenotypes in autism, as it has already been mentioned above. Neural tissue is more susceptible to this enhanced growth during the period of neurogenesis.

It is thus proposed that autism is the result of epigenetic disruption in brain development caused by gestational exposure to these conditions (which interfere with neurogenesis).

So, it is hypothesized that autism is the physiological and ecological cost that is paid for the enhanced growth rate activation, especially in neural tissue, due to increased resource and energy availability during the prenatal and postnatal period of increased plasticity (excess numbers of neurons are produced but they are also liable to impairment). In other words, it is proposed that autism may represent an adaptive response to modern urban "environmental abundance".

It is clear that there is a limitation of this study. ASD is a highly complex condition: heterogeneity

runs through all over the disorder from its etiopathogenesis to phenotypic expression and prognosis. This means that many genetic, epigenetic and environmental factors are responsible for the increase of autism prevalence today and every autism case must be individualized. So, it is rational for every hypothesis that tries to explain such a complex condition, not to be applicable to all autism cases. This hypothesis could be more suitable for those cases where overgrowth (for example macrocephaly) pattern predominates. An early developmental enlargement of brain volume, including macrocephaly, (which is frequently associated with poor prognosis), occurs in about 20-30% of idiopathic ASD [138]. Consequently, this hypothesis could explain the 20-30% of autism cases. Other factors and hypotheses can answer for other groups of autistic children, for example for those of low weight.

Finally, it is obvious that both abundance / overgrowth and deprivation / undergrowth could result in pathological conditions. Either abundance or deprivation during the critical embryonic period (when neurosensitivity and neuroplasticity are very high [139]) are specific environmental stressors that can alter gene expression (epigenetic programming) resulting in an alternate phenotype that is better suited for an adverse environment.

8. CONCLUSIONS

This paper may introduce a novel consideration about autism causation. In particular, several different autism characteristics (phenotypic, such as macrocephaly, megalosomy, obesity and laboratory, such as BDNF, IGF-1, IGF-2, IGFBP-3, GHBP, leptin, testosterone, oxytocin) and some autism risk factors (such as maternal metabolic conditions, prenatal and postnatal nutritional supplements, infant milk formula and breastfeeding) are viewed through the lens of a unified consideration: the increased availability of resources and energy to the developing fetus and the subsequent increased activation of its growth pathways, especially at neural tissue.

This causation model may be able to explain the increase in autism prevalence in urban areas during last decades.

It is thus proposed that autism is the result of epigenetic disruption in brain development caused by gestational exposure to these conditions (which interfere with neurogenesis).

So, it is hypothesized that autism is the physiological and ecological cost that is paid for the enhanced growth rate activation, especially in neural tissue, due to increased resource and energy availability during the prenatal and postnatal period of increased plasticity (excess numbers of neurons are produced but they are also liable to impairment). In other words, it is proposed that autism may represent an adaptive response to modern urban “environmental abundance”.

It is clear that multiple, long-lasting, detailed studies are required to confirm such a hypothesis. Autism researchers, also, have to utilize knowledge from diverse disciplines (evolutionary, biology, nutrigenomics, methylomics, phenotypic plasticity, physical anthropology) in order to more precisely define the risk factors that are responsible for the programming of autism spectrum disorders.

If, however, these observations and concerns are confirmed, a holistic approach of childbirth would be possible and well organized preventive programs (about parental health and nutrition before conception, nutrition of pregnant woman and child, optimal breastfeeding, rational use of nutritional supplements, etc). could be carried out.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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