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ALLOSTATIC LOAD AND CHILDREN'S DISEASE

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Abstract: *Allostatic (over)load appears to be a substantial cause of morbidity for adults. For children, new aspects emerge. They are particularly significant for their repercussions in childhood and adult life: obesity, metabolic syndrome, arterial hypertension, insulin resistance, or eating disorder. It is desirable to identify clusters relevant for certain diseases to prevent long-time and irreversible consequences of allostatic load.*

INTRODUCTION

Allostatic load refers to the cumulative biological effects which occur in an organism under chronic stress or acute and constant stress. It is a measure of the dysregulated response of the body to stress.(1,2)

This parameter is not only a biological measure, but a social one, being able to predict the way in which certain individuals will develop according to a certain level of the allostatic load. The development refers to different health aspects, such as cardiovascular disease, diabetes, obesity, asthma, autoimmune disorders, depression or cognitive decline. Over the years many factors were studied in relation to allostatic load. In Europe, they were mainly related to gender, ethnicity, neighbourhood's socioeconomic status and social and occupational hierarchy.(3) There are few studies on this subject in children and they are focused on mistreatment, bullying, maternal deprivation, and neighbourhood's socioeconomic status. Only some of them refer to the allostatic load and chronic disease that emerge in childhood.(2) Therefore, many aspects remain to be clarified in the coming years.

Stress, homeostasis and allostasis

The notion of ***stress*** is highly individualized, difficult to define and measure. Whether the danger is real or imaginary it can induce changes in the human physiology, biology, behaviours and environment. The stress can be beneficial if it can be controlled using coping abilities, or can be overwhelming. The perception of stress is modulated by genetic factors, personal experience and behaviour.(4,5)

Allostasis refers to "the ability of complex physiological systems to maintain stability or homeostasis through change".(4)The notion is attributed to Sterling and Eyer and has emerged since 1988.(4,6) The term derived from the Greek "allo" that means "variable" and "stasis" that means „stand". It involves complex adaptation mechanisms of internal parameters due to different challenges (physical, social, environmental etc.) and a "stress response" which implies a flow of inflammatory cytokines, adrenal hormones and other profound biological changes.(4,6) Therefore, allostasis is an active process of maintaining ***homeostasis*** defined as essential parameters of life (5) or "a condition which may vary, but which is relatively constant."(7)

Allostatic load is a concept introduced in 1993 by Ewen and Stellar and refers to the failure of allostatic mechanisms resulting in chronic dysregulation of physiological systems.(4) The brain has the leading role in both allostasis and allostatic load. It is capable to control a lot of mechanisms in the same time and also to modulate physiologic and behavioural responses. In chronic or repetitive stress, the autonomic nervous system and hypothalamus – pituitary axis are activated leading to an overflow of stress hormones, such as cortisol, epinephrine, norepinephrine, DHEA, prolactin, growth hormones and also dopamine responsible for the inflammatory damage.(1,4,5,6) To these processes participate receptors for steroid hormones and messenger systems for cathecolamines.(5) The brain itself is altered in both structure and chemical function. Once a hormone is secreted, they have short and long term actions. The short-term actions are mainly responsible for allostasis and the long term ones are responsible for allostatic load and tissue damaging.(5) Therefore, allostatic load can be defined as "cumulative results of allostasis".(4,5,6)

Allostatic overload refers to an extreme state in which "stress response systems are repeatedly activated and buffering factors are not adequate".(8) Two types of allostatic overload can be described: type one in which the organism lacks the energy and the nutrients for a normal function and type two in which the organism has a exceed of energy or nutrients and needs to store them which overloads the normal functional systems.(5)

Consequences of the allostatic (over)load

As a response of the challenges that act on the human body, physiological systems are activated. The most important systems interact, modifying the architecture and the function of the human body. These are detailed as follows:

- Brain architecture and neurochemical functions are altered. These modifications as related with decline in cognitive functioning, mood and anxiety disorder or psychotic disorder.(8,9)
- Cardiovascular system – allostatic load is linked to a higher

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risk for cardiovascular disease such as coronary and peripheral arterial disease. One in three persons with allostatic overload has been diagnosed with essential hypertension, almost five percent of the patients with implantable cardioverter defibrillator have severe allostatic overload, which is a predictor for negative cardiac outcomes.(8)

- Immune system suffers adjustments in order to adapt, which are related with an immunosuppressive state as a long time effect.(8)
- Metabolic and endocrine adjustments, including activation of hypotalamus-pituitary axis are correlated with the onset of type 2 diabetes, breast and ovarian cancer due to cortisol excess, obesity and metabolic syndrome.(8)
- People with allostatic overload make poor life-choices, such as alcohol or drug abuse.(8)
- In general population, higher allostatic load is associated with poorer health outcomes.(8)

Measuring the allostatic load

The MacArthur Studies proposed that allostatic load should be evaluated by an index including 10 parameters. These parameters reflect the activity of the four major systems involved: neuroendocrine, metabolic, cardiovascular and immune. Over the last years, this index suffered some modifications in the number (6-17) or the type of biomarkers.(10,11,12)

The initial list of 10 parameters included primary and secondary mediators.

- Primary mediators of allostatic load – related to the adrenal activation and are chemical messengers released as part of allostasis include cortisol, dehydroepiandrosterone (DHEA), epinephrine and noepinephrine.(2,5,8,10)
- Secondary mediators – related to secondary outcomes include colesterol, glicosylated hemoglobin, resting systolic and diastolic blood pressure, body-mass index, waist-hip ratio.(2,8,10) Waist-hip ratio is an index of increased glucocorticoid activity.(5)
- Tertiary mediators are biological markers of diseases induced by allostatic load. Glucose levels, lipid profiles, IL-6, heart rate variability are included in this category.(5,8)

The index represents the sum of each of the 10 parameters included. Higher the value of the score show higher physiological response.(10,13)

The vast majority of the studies on this topic have included adult populations. In younger populations, the attempts are still timid. For younger individuals, the allostatic load gets a new dimension. It is more likely that allostatic load is related to severity of stress and not its duration. In addition to this, adolescence is a period of transition from childhood to adulthood and is characterized by high sensitivity, making adolescence a difficult period. The utility of the original score for allostatic load has not been established for children and adolescents.(10) Although there is no consensus concerning the utility of these parameters in children, recent studies show that the factors measuring metabolic dysregulation, including BMI and waist-hip ratio appear to be the best indicators for allostatic load in adolescent population.(4,14)

Most of the studies made so far highlight the necessity to include in the evaluation of allostatic load more secondary outcomes. The parameters proposed for this purpose are:

- Cardiovascular risk can be evaluated by fibrinogen and nitric oxide;
- Immune system – delayed type hypersensitivity and immunization challenge, the frequency and severity of common cold;
- Identifying clusters relevant for certain diseases.(5)

Factors that contribute to allostatic load in childhood

Preterm birth is a very complex health issue and is considered a medical challenge. The rate is over 10% and increasing worldwide, in more than 50% the cause remains unknown and recent studies show that allostatic load might be „both a risk and a causal factor". An intrauterine pro-inflammatory state is considered a marker for preterm birth.(6) The causes of this inflammatory state are numerous, such as genetic factors, infection, rupture, stress and make the transition of the uterus from an anti-inflammatory state to a pro-inflammatory one. In terms of activity, the uterus is transformed from pro-pregnancy to pro-labour. All these inflammatory sequences are mediated by pro-inflammatory cytokines and chemokines – IL-1β, IL-6, cellular adhesion molecules (CAMs), prostaglandins and matrix metalloproteinases (MMPs).(6)

Elevated allostatic load appears to be related to a shorter gestation length, and women who delivered preterm had a higher allostatic load scores when compared to those delivering on time.(6,8,15) Research is currently being done to develop a prognostic test including allostatic load and preterm birth.(6) In these circumstances, two major aspects emerge - the allostatic load of the future mother and of the new-born facing a very stressful life event.

Allostatic load in children was correlated with ***early menarche, violence*** and ***adolescent alcohol use***, but also with ***eating disorders***. Allostatic load is more elevated in children and adolescents with higher cumulative risk. Cumulative risk includes physical factors, environmental factors (poverty, single parenthood) and psychosocial factors.(4)

Early-life socioeconomic position is considered a "determinant of physiological wear and tear through allostatic load" and disadvantaged childhood is associated to a "slower cortisol recovery after a cognitive-stress challenge".(12)

Adverse childhood experiences such as trauma or abuse appear to induce alterations in brain structure and stress-response systems.(12)

Allostatic load and childhood disease

Asthma – the link between stress and asthma is very complex. Children are more likely to develop asthma if they were exposed to maternal stress in early childhood.(16)

High allostatic load is associated with a 4.6 times risk to atopic asthma by the age of 12 years for boys, but not for girls. Boys are at risk for nonatopic asthma if they have higher allostatic load, while girls do not show association between allostatic load with either atopic or nonatopic asthma.(2)

Overweight and obesity

Recent studies show that in children there is a strong association between high allostatic load and overweight or obesity. Also, for overweight and obese children allostatic load is a very important factor for morbidity. Obesity itself is considered a stress inducer by altering the homeostasis. There is no sufficient data to support the hypothesis that obesity is the source and not the result of stress.(17,18)

Mechanisms involved are complex. Obesity is correlated with a low-grade chronic inflammation and high levels of pro-inflammatory cytokines such as IL-1, IL-6, TNF, plasminogen activator inhibitor-1, C-reactive protein that lead to an activation of hypothalamus-pituitary axis and high levels of cortisol. The same effect has the high levels of leptin associated with obesity.(17)

Metabolic syndrome was correlated with high allostatic load in children. The identified aspect refer to abdominal obesity, insulin resistance, hypertriglyceridemia and high blood pressure.(17,18)

Regarding the biomarkers that were monitored, the ***conclusions for children*** are detailed as follows:

- Abnormal cortisol is more frequent in boys with nonathopic asthma;(2)
- Hypercholesterolaemia is strongly associated with new-onset asthma in boys;(2)
- In girls, nonatopic asthma is inversely associated with serum glucose;(2)
- Boys with high levels of at least two biomarkers are at higher risk to develop new-onset asthma by adolescence;(2)
- In boys with high levels of cholesterol and glucose are associated with a five times higher risk for atopic asthma;(2)
- High levels of cortisol and serum glucose induce a 8 times risk for nonatopic asthma for boys;(2,18)
- Glucose intolerance and insulin resistance associate with obesity induce airway hyperreactivity in pre-pubertal children;(19,20)
- Hyperglycemia is a common finding in children hospitalized with acute asthma and "could be considered as a marker of a longer hospital stay";(20,21)
- High levels of low- density lipoproteins are associated with increased risk of asthma at age 7 years;(22)
- Children with high allostatic load have higher levels of triglycerides, PCR and calprotectin when compared to subjects with low allostatic load.(3,20)

The interpretation of these biomarkers should be made with precaution because many of them are influenced by total body adiposity and may not be fully associated with allostatic load.(2)

CONCLUSIONS

For children, allostatic load needs further studies to determine the exact dimension, short-term and long-term repercussions. It is expected that this notion will explain many pathological conditions in the years to come for both children and adults.

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