STRESS IN PEDIATRIC PATIENTS – THE EFFECT OF PROLONGED HOSPITALIZATION

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LONG-TERM HOSPITALIZATION, STRESS IN PEDIATRIC PATIENTS, CHROMOGRA NIN A, SALIVARY ALPHA AMYLASE.

STRESS IN PEDIATRIC PATIENTS – THE EFFECT OF PROLONGED HOSPITALIZATION (Abstract): Long-term hospitalization emotionally impacts any patient, especially children, and is defined as a long period of time during which the patient is hospitalized and experiences isolation from his or her family, friends and home. Stressful situations trigger a nonspecific response that involves multiple physiological mechanisms. Currently, because of the complexity of these mechanisms, there are no laboratory markers that allow the quantification of the stress intensity felt by the patient. Laboratory determinations currently used in evaluating the response to stress are neuroendocrine, immunological and metabolic. The neuroendocrine system is the first to respond to stressful events. Stress stimulates the hypothalamus, leading to the release of CRH, which stimulates the pituitary gland to produce ACTH. Chronic stress directs the synthesis towards cortisol, which may lead to hypo secretion of the other adrenal steroid hormones. The hospital and the disease are stressors for children and caregivers, since stress can interfere with the normal development of young patients, affecting them in the long term. Admitting a child to hospital means interrupting his or her normal daily life and changing the environment that is familiar to him or her. Therefore, the involvement of the family doctor is very important, as many conditions can be solved by visiting his or her office and thus eliminating the need for hospitalization in a pediatric hospital. If, however, the nature of the condition requires that the child should be seen by a pediatrician, the period of hospitalization should not be much extended so as to prevent the appearance of other possible problems that might influence the child’s state. Keywords: LONG-TERM HOSPITALIZATION, STRESS IN PEDIATRIC PATIENTS, CHROMOGRA NIN A, SALIVARY ALPHA AMYLASE.
talization involves not only a particular period of time, but also the moment when a person loses emotional balance. Pediatric patients are in the process of determining their own identity, and they are psychologically, emotionally and physically dependent on their family and friends. Fortunately, medical advances have increased survival rates, while decreasing mortality rates. Children go through “normal developmental stress”, doubled by the negative impact that the long-term hospitalization can have on their neuropsychological, emotional and physical development (1).

Compared to adults, infants and young children are significantly influenced by the hospital environment and its adjacent factors. Children’s lack of proper and full understanding of what is happening, their communication skills that are insufficiently developed to transmit their needs, as well as their emotions and experiences may often go unnoticed by caregivers. At the same time, young patients’ state of anxiety increases (2).

For all patients, temporarily giving up their personal belongings, intimacy, entourage and known environment, trigger anxiety. Wearing a certain outfit during their hospital stay, sleeping in a different bed, being imposed a certain program, diet, medication, as well as going through all the tests increases stress. On top of all this, patients come into contact with many strangers; this causes them to feel deprived of almost all aspects related to their personal space. Patients find themselves in an unfamiliar environment, which is worrying for most adults, and especially for children. In addition, hospitalization has different effects on newborn patients’ long-term development, compared to adolescent patients (2, 3). Infants often get scared by unexpected noises, sudden maneuvers and movements. Starting with the age of 6 months, children already have a strong attachment towards the people who take care of them (and especially towards their mothers). Separation from these people can generate a significant discomfort in young patients, leading to the fear of separation. Moreover, children begin to be afraid of strangers and of people with atypical appearance or traits they are not used to (e.g., people wearing protective masks on their face). Up to 1 year, children acquire a lot of new skills; if they are admitted to hospital for a long period of time, developmental delays may occur. They may lack the sensory stimulation that would help them develop (music, light, reading stories, playing with the people who take care of them, toys, etc.). If parents do not spend enough time with their children in hospital, the relationships between them can be affected. The development of children aged between 1-2 years may be delayed due to the fact that the time spent in hospital interferes with the activities that could help stimulate new skills. Sleep problems may occur (2, 3, 5). Dietary imbalances are a result of home routine change and stress. At this age, children are very afraid of strangers, thus the presence of nurses and doctors increases their level of anxiety. Children are irritated, frustrated and frightened because, at this age, it is hard for them to understand why they are hospitalized. For children between 2-5 years, the main negative impact is the stress of being away from everything that is familiar to them. They may exhibit phobias towards medical procedures, which are perceived like something that can hurt them; they also feel threatened, restricted, punished and tortured (1, 3). They may feel that they have done something wrong and that this is why they are in hospital. They roughly know their bodies, but their under-
standing on how the body works is far from clear to them, and this can create frustration. Language is largely developed by the age of 5 years, but children may misinterpret what they hear. Starting with the age of 2-3 years, children begin to have the conscience of the self and their fears start to become somewhat specific. In general, at this age stage, children are afraid of things or phenomena they do not understand or cannot control (3, 6). Young children have a limited understanding of the dimensions of the things surrounding them and of the relation between cause and effect, which triggers irrational fears. The fear of separation from the people who take care of them is still present at this age. Other fears that appear are the fear of large animals, of water, of the unknown and of pain. Children’s active imagination and their limited ability to distinguish between real and imaginary things cause them to be afraid of real characters. Between 3 and 6 years old, children are often afraid of being left alone or getting lost from parents. They are afraid of things such as insects, darkness, noise and actions they cannot explain or they have not come across with, imaginary creatures, physical injuries, going to the doctor, thunder and lightning (3, 7). Children aged 5-12 years may experience any of the states listed above, plus the fact that, during this period, they show normal fear of doctors, needles and pain. As children learn more about the complexity of the world that surrounds them, many childhood fears disappear; yet, they are replaced by other fears. As children’s social life becomes increasingly important, many fears appear which are related to their way of interacting with other children and even with adults. In addition, abstract thinking gradually begins to develop, and children’s fears also “shift” from concrete to abstract things. Fears gradually shift from the present to the future and from the certain to the hypothetical or the potential (2, 6, 7). Children begin to fear that someone in the family could be hurt or die. Other fears appear, i.e. the fear of being rejected by other children or not having friends, being ridiculed, humiliated, as well as the fear of not meeting the expectations their parents or other adults (e.g. teachers) might have related to their performance (at school or in other activities) (3, 4). Other fears continue to be normal, such as the fear of doctors and of medical procedures, the fear of natural disasters and, in general, of any potentially destructive phenomenon over which the child has no control. In addition, what is new is the appearance of a certain discomfort caused by the invasion of own privacy. As children grow, they begin to understand that they are suffering from a serious illness or that something bad is happening, with major physiological consequences. Chemotherapy, medical tests, surgery, invasive maneuvers cause a constant fluctuation of the stress level in children. Some children tend to associate the restriction of movement with death, while for older children the loss of interaction represents the isolation from the processes of everyday life (5, 7).

The combination between these states and the boredom caused by the interruption of the activities that children were used to doing can cause extreme rises in the levels of anxiety and stress. Some children, after being hospitalized for a long period of time, may exhibit low self-esteem and a distorted image of own body. They may feel harassed and ignored to such an extent that they end up feeling unprepared for the transition back to normality. Because of a severe diagnosis and of prolonged hospitalization, some children and adolescents may
feel incapable of keeping up with school activities; they may feel marginalized and “left behind” (3, 4, 5). Isolation and emotional regression are also serious consequences of an illness occurring in childhood. After setting the diagnosis and initiating the treatment of a serious illness, such children often tend to become more mature than their friends. At school, it is difficult for them to find friends with whom they can socialize. Their health status often limits their participation in sport activities and causes them to end certain relationships, feel lonely and emotionally isolated. In addition, their school performance declines (2, 7). Given the factors causing isolation and a bad self-image, these patients may show depressive disorders from an early age. The complexity of fears in adolescence reflects the cognitive level and the physical and mental transformations specific to this stage. Adolescents are afraid of academic failure, parents’ disappointment and rejection from friends. They are also afraid they might be put in an unfavorable light or ridiculed in front of others. In addition, they are worried about physical imperfections (e.g. acne, too high or too low body weight), death, physical and emotional harassment. During this period, great emphasis is placed on physical appearance, self-image, other people’s opinion about them, the feeling of belonging to a group and peers’ acceptance, as well as individual performance (3, 5).

**Stressful situations trigger** a nonspecific response that involves multiple physiological mechanisms. Due to the complexity of these mechanisms, there are still no specific laboratory markers that allow the quantification of stress intensity experienced by the patient. Laboratory determinations currently used in evaluating the response to stress are neuroendocrine, immunological and metabolic. The neuroendocrine system is the first to respond to stressful events. Stress stimulates the hypothalamus, leading to the release of CRH (corticotropin releasing hormone), which stimulates the pituitary gland to produce ACTH (adrenocorticotropic hormone). Under the action of ACTH on the adrenal gland, adrenaline and norepinephrine are released (from medulla) along with cortisol (from cortical area) (8). Chronic stress directs the synthesis towards cortisol, which may lead to hyposecretion of the other adrenal steroid hormones.

Cortisol exerts immunosuppressive and anti-inflammatory effects. Secretion of cortisol has a circadian rhythm, with elevated levels in the morning. Cortisol levels peak 20-40 minutes after acute stressful events. Cortisol blood levels are influenced by other factors (genetic factors, obesity). Cortisol may be measured in urine, saliva and serum, but salivary cortisol is often considered a better marker. In saliva, cortisol appears mainly in free form, not bound to proteins (such as blood); it is relatively resistant to the enzymatic degradation and it is unaffected by the salivary flow concentration. In addition to that, the procedure is less invasive (9,10).

**Catecholamines:** adrenaline and noradrenaline are secreted by the adrenal medulla in response to the stimulation of the sympathetic nervous system. The blood peak is recorded 60 minutes after the stressful event. The measurement of catecholamine levels in saliva requires immediate processing, as catecholamines are rapidly oxidized (9).

Salivary alpha amylase represents the major salivary protein (40-50% of the total proteins) and it is considered a marker of the sympathetic nervous system activity. The determination of salivary alpha amyl-
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Chromogranin A is a protein with a single polypeptide chain, rich in acidic amino acid residues, which belongs to a family of neuroendocrine secretory protein named cromogranins / secretogranins. These proteins are located in the secretory vesicles of the neurons and the endocrine cells. The largest amount of chromogranin A is found in the granulations of the adrenal chromaffin vesicles and of the sympathetic nervous system. Chromogranin A is considered a stress hormone and the precursor of a number of peptides with biological functions (vasostatin, pancreastatin, catestatin, parastatin) with roles in inflammations and oxidative processes. It is associated with increased sympathetic nervous system activity induced by psychological stress (11).

Submandibular salivary glands secrete Chromogranin A, making it possible for it to be measured in saliva. The correlation between blood and salivary concentrations is not yet fully understood. A circadian rhythm has been described for human subjects, with peaks around 11 pm and minimum levels around 8 am.

Salivary chromogranin A level changes faster and is more sensitive to psychological stressors compared to salivary cortisol. After the cessation of the stress factor, chromogranin levels quickly return to the basal state (12).

Cytokines. Initially, it was assumed that stress had an immunosuppressive effect, thus explaining the infections and malignancies reported in people subjected to chronic stress. Recent studies have changed the concept of stress seen as an immunosuppressive factor, considering stress as an immunomodulatory process. These studies have focused on measuring the levels of cytokines secreted by Th1 and Th2 lymphocytes. Th1 cytokines (IL-2, TNF alpha, interferon gamma) are involved in cell-mediated immunity, while Th2 (IL 4, IL 5, IL 9 IL10) are involved in the humoral-mediated immunity. Stress affects the secretion of both types of cytokines; these cytokines are involved in the pathophysiology of inflammatory diseases (rheumatoid arthritis, asthma). Studies have proved that stress does not suppress, but acts differently on the cytokines secreted by Th1 and Th2.

Acute stress events determine a decrease in Th1 levels and an increase in Th2 cytokines levels; since Th1 cytokines are involved in cell-mediated immune response, this would increase the vulnerability to viruses and bacteria. Chronic stress leads to decreased Th1 and Th2 levels. Stress hormones, especially cortisol, affects the differentiation of naive Th0 cells into Th1 and Th2 with inhibitory effects on Th1 and potentiating effects on Th2 cytokines. Glucocorticoids suppress the production of IL12 by antigen-presenting cells (IL12 is necessary for the transformation of Th0 into Th1) and decrease the expression of IL 12 receptors by T cells and natural killer lymphocytes. They prevent the production of IFN gamma by Th1 lymphocytes stimulated by IL12. Glucocorticoid hormones also induce the production of IL 4 and IL 10. Studies have reported that chronic stress may lead to low levels of cortisol. A possible explanation could be the cortisol resistance theory: high levels of cortisol determine a decrease in the number of receptors (down regulation), which leads to
the inability of the immune system to respond to chronic stress.

It is difficult to determine the levels of cytokines, because they degrade rapidly in the tissue, thus reaching the bloodstream in small amounts. Ongoing infections and exposure to allergens also influence the basal cytokine concentrations (13, 14, 15).

CONCLUSIONS

Following the evaluation of the bibliographic information, which added to our clinical experience, we have concluded that children's admission to hospital involves changing their familial and familiar environment. Both the hospital and the illness are major stressors for children as well as for their caregivers, as stress can interfere with the normal development of pediatric patients and it can affect them in the long term. Admitting a child to hospital means interrupting his or her normal daily life and changing the environment that is familiar to him or her. Therefore, the involvement of the family doctor is very important, as many conditions can be solved by visiting his or her office and thus eliminating the need for hospitalization in a pediatric hospital. If, however, the nature of the condition requires that the child should be seen by a pediatrician, the period of hospitalization should not be much extended so as to prevent the occurrence of other possible problems that might influence the child’s status.

REFERENCES

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MYOEPITHELIAL CELLS (MEC) OF THE SALIVARY GLANDS IN HEALTH AND TUMOURS

In many exocrine organs, the secretory end pieces and the ducts are partly covered by cells with long processes that form an interlacing network. These cells resemble smooth muscle cells in several important aspects, yet clearly are epithelial cells, and thus are referred to as myoepithelial cells (MEC). The MEC were first discovered in the breast tissue by Krause in 1865. Since then it has been observed in the terminal end pieces and ducts of most of the exocrine glands such as salivary, mammary, sweat, lacrimal and bronchial glands. The description of these cells is diverse. Various authors have described them as “spindle shaped cells”, “star shaped cells” or “basket cells” until the term “myoepithelial cells” was conferred to it. Most of the authors have studied this cell in detail in the mammary glands only until it was Tamarin in 1966 that provided a vivid image of a typical acinus-associated MEC in the salivary gland. He typically described the appearance of the cell on the acinar unit as being “like an octopus sitting on a rock”. These cells lie between the basal lamina of the acinar and ductal cells at the terminal portion of the salivary glands. Positive identification of salivary gland MEC on routine microscopic preparations is very difficult. Fortunately modern sophisticated microscopic techniques have resulted in a surge of new information on this cell such as exposure of MEC by chemical removal of periacinar connective tissue and basement membrane deposits. MEC have many cytoplasmic processes which embrace glandular cells. Their nuclei are localized in the cell body. Most of the cytoplasmic organelles are found in the small areas around the nucleus. The remainder of the cytoplasm is filled with filaments and vesicles which are morphologically similar to those found in smooth muscle cells. After studying the structure of MEC in detail researchers focussed on identifying the physiological functions of these cells. The function of MEC was identified by an essential term in biologic kinetics (kinesiology) which states “form defines the function”. The shape of the MEC suggested that its contraction might reduce the luminal volume in glandular endpieces, and these cells may play a role in expelling secretory products from glandular endpieces to the excretory duct system which was later proved experimentally. Thus one of the chief functions of MEC was determined. Association of tumours with MEC was determined when scientists found that a variety of tumours occurred in salivary glands and breast as compared to pancreas and concluded that this was because of presence of MEC in the former two glands. In conclusion, this paper brings about a thorough description of this cell in both physiological and pathological aspects (Chitturi RT, Veeravarmal V, Nirmal RM, B. et al. Myoepithelial Cells (MEC) of the Salivary Glands in Health and Tumours. Journal of Clinical and Diagnostic Research. 2015 Mar, Vol-9(3): 14-18).

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