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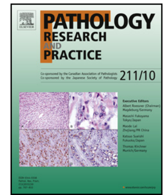

Original Article

Morphological and inflammatory changes in the skin of autopsied fetuses according to the type of stress

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ABSTRACT

Introduction: The fetal skin acts on the development and activation of the immune response via immune–neuroendocrine communication coordinated by corticotropin-releasing hormone.
Objective: This study aimed to evaluate the morphological and inflammatory changes in the skin due to acute stress and chronic stress, associated with perinatal asphyxia, ascending infection and congenital malformation.
Methods: We measured dermal and epidermal thickness, the diameter of keratinocytes, and the percentage of collagen and elastic fibers. Immunohistochemistry was used to evaluate both Langerhans cell and mast cell density, and corticotropin-releasing hormone expression in the epidermis, sebaceous gland, sebaceous duct, sudoriparous gland and in the hair follicle.
Results: The epidermis was thinner in the cases with perinatal asphyxia, ascending infection and chronic stress. The diameter of keratinocytes was smaller in ascending infection and chronic stress. Mast cell density showed an indirect correlation with gestational age. Corticotropin-releasing hormone expression was significantly higher in ascending infection and chronic stress.
Conclusions: Chronic stress is associated with immunological and morphological changes in the skin of fetuses with perinatal asphyxia and ascending infection. Thus, corticotropin-releasing hormone seems to play a vital role in the differentiation and activation of innate and adaptive immune cells of the skin of fetuses.

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1. Introduction

Human skin is the largest organ of the human body, and it plays a key role in the protection against pathogens and in body temperature control [1,2]. The embryonic development of the epidermis and the dermis occurs between 3rd and 30th weeks of gestation [3,4], and in the 34th week the fetal skin has a similar architecture to the skin of a newborn term infant or an adult [4].

The epidermis is structurally composed of keratinocytes organized in the following layers: cornified, granular, spinous and basal layers. Melanocytes promote pigmentation [5,6], and Langerhans cells (LC) contribute to the immune response of the skin [2,7]. The dermis is composed of an organized network of collagen and elastin fibers [5], blood vessels, sebaceous glands, mast cells, hair follicles, nerve fiber bundles and fibroblasts [1,2,8].

During intrauterine development, the skin acts in the initiation and activation of immune response via a coordinated neuroendocrine communication network between epidermal cells, dermal cells and lymphocytes [1,2,7]. This cell response allows for the activation and recruitment of immune system cells and for the synthesis of the inflammatory mediators [9–11], such as cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [1,2,9,12,13].

Gestational changes induce perinatal stress, thus leading to the development of functional compensation mechanisms and

Abbreviations: AS, acute stress; CS, chronic stress; CM, congenital malformation; PA, perinatal asphyxia; AI, ascending infection; CRH, corticotropin-releasing hormone.

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morphological changes in various fetal organs, for instance, the suprarenal gland and the placenta [14]. In the central nervous system, stress is capable of activating the hypothalamic-pituitary-adrenal axis (HPA) and increasing cortisol synthesis [1,12,15,16] in response to adverse intrauterine stimuli, such as hypoxia [14,17], premature birth [18] and infections [19].

This classical pathway is activated through the hypothalamic synthesis of corticotropin-releasing hormone (CRH). CRH receptors, CRH-R1 and CRH-R2, stimulate the pituitary gland to secrete proopiomelanocortin (POMC)-derived neuropeptides [20,21], such as the adrenocorticotropic hormone (ACTH), which stimulates melanocyte-α (α-MSH) and β-endorphin; these neurotransmitters act on melanocortin receptors and β-endorphin receptors, respectively, as well as stimulate the synthesis of cortisol in the adrenal gland. The HPA axis may also be stimulated by inflammatory mediators released after activation of innate and adaptive immune system, for instance, by psychotropic drugs, neoplasias, pregnancy, and obesity [21].

Fetal skin is capable of activating this neuroendocrine pathway. Follicular and epidermal keratinocytes, melanocytes, fibroblasts, endothelial cells and smooth muscle of blood vessels, for example, synthesize CRH, POMC, its neuropeptides, receptors CRHR-1 and CRHR-2 [2,13,16,20,22], as well as other hormones and receptors, such as catecholamines, acetylcholine, and neurotrophin and neurokinin receptors. Similar to what was observed in the HPA axis, the response to stressful factors becomes highly synchronized by the mediators, which modulate the inflammatory response [1,2,16,18,22].

The interaction of CRH and ACTH via specific receptors on epidermal and dermal cells is able to stimulate the expression of genes for cytochromes P450c17, P450c21 and MC2-R, for instance, in order to allow for the synthesis of key enzymes in the metabolism of glucocorticoids, such as cortisol. A secondary pathway, formed by direct stimulation of CRH-R by CRH, as well as the synthesis of POMC without the participation of CRH or CRH-R1, may also be triggered depending on the location of the target cell and on the prevalence of a particular receptor in cutaneous neuroendocrine response [2].

Thus, a cutaneous stress response system responsible for modulating cutaneous immune response independent from the HPA axis is acknowledged. The action of physical chemical, or biological injury, or of inflammatory mediators stimulate the local synthesis of CRH and POMC-derived peptides [2], which induce the maturation and degranulation of mast cells, promote scarring and vasodilation, interfere in the proliferation and differentiation of keratinocytes, and in fibroblast activity [1,2], among other things.

We hypothesized that there is a strong inflammatory response associated with this neuroendocrine pathway in response to the stressors, impacting on morphology and inflammatory mediators that act on the skin, especially in cases with a greater response to prolonged perinatal stress.

Therefore, this study aims to evaluate the morphological and inflammatory changes in skin due to perinatal stress associated with various causes of death.

2. Materials and methods

2.1. Subjects

This study was approved by the Triângulo Mineiro Federal University Research Ethics Committee, approval number 1797. We selected pediatric autopsy protocols from the Discipline of General Pathology at the Federal University of Triângulo Mineiro, Minas Gerais, Brazil, 1994–2012. All the cases were in the perinatal period, that is, with gestational age (GA) ≥22nd weeks up to the seventh day of birth. We excluded 104 cases with incomplete records, blocks and slides not available in the archives; cases of autolyzed skin. In this study, we evaluated 48 cases.

2.2. Groups

The cases were classified according to perinatal stress. Perinatal stress was defined when the thymus, adrenal, and liver presented morphological alterations compatible with intrauterine stress [14] and cause of death [23]. The adrenal presented increasing amounts of coarse lipid droplets in the fetal cortex. The thymus was evaluated according to the presence of phagocytosis (positive cells for CD68 antibody), cortex thickness, and the weight for involution. The amount of intrahepatic hematopoiesis was evaluated in the liver. The cases were subdivided into two groups: (1) acute stress (AS): characterized by events occurring at or after birth that might have been the causative agent of fetal death, including cases with congenital malformation (CM) [24]; (2) chronic stress (CS): defined by the response to injuries of long duration which begin in the intrauterine period and remain until birth, and that may be related to the pathogenesis of perinatal death, including cases of perinatal asphyxia (PA) and ascending infection (AI) [14]. In these groups, all the cases were matched according to the GA.

2.3. Collection of study material

Skin sections of the thoracic region were recovered from the sample file and were fixed in formaldehyde 10%, dehydrated in alcohols, diaphanized in xylol, and embedded in paraffin. Then serial 4 μm sections were cut.

2.4. Morphometric analysis

(1) Epidermal and dermal thickness: the histological sections were stained with Hematoxylin & Eosin. Images of 13 sections of epidermis and the whole dermis were captured using Leica QWin Plus® software (Leica Microsystems, Inc., Wetzlar, Germany). Thickness (μm) was measured using ImageJ® software (NIH, Bethesda, Maryland, US), by performing five measurements per field, one central measurement, two edge-to-edge measurements, and two measurements of equidistant points between the central and edge measurements; (2) mean cell diameter: obtained by dividing the thickness of the epidermis by the number of epidermal cell layers; (3) quantification of collagen and elastic fibers: for each component, the sections were stained with Picrosirius and Verhoeff, respectively. Leica QWin Plus® software was used for the quantification, hence obtaining the percentage of these fibers per analyzed field area.

2.5. Immunohistochemistry technique

(1) Antigen recovery: it was performed using trypsin (Sigma–Aldrich®, Inc., St. Louis, MO) for mast cells, and using citrate buffer pH 6 for LC and CRH. (2) Endogenous peroxidase blocking: it was performed with 0.05 M PBS and H_2O_2 (5%) for 45 min for LC and mast cells, and methanol and H_2O_2 (3%) for 45 min for CRH; (3) primary antibody: anti-S100 (1:400; Dako®, Inc., Glostrup, Denmark) was used for LC, anti-mast cell trytase [AA1] (1:1000; Abcam®, Inc., Cambridge, UK) was used for mast cells, and anti-corticotropin-releasing factor (1:60; Novus Biologicals®, Inc., Littleton, CO) was used for CRH. Finally, NovoLink™ Max Polymer Detection System (Leica Microsystems, Inc., Wetzlar, Germany) was used.

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