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INTERNAL AND EXTERNAL FACTORS RELATED TO BRACHYCEPHALY: AN INTEGRATIVE REVIEW

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ABSTRACT

Prenatal and gestational factors influence embryonic formation directly and indirectly. Its capabilities to influence cranial malformation are the subject of research around the world and a global understanding of this influence is needed. The present review seeks to compile and correlate the internal and external factors responsible for the presence of brachycephaly. To this end, studies were selected that were divided into two groups of triggering factors: external and internal. The literature contemplates that among the external factors: the maternal smoking habit, the time of delivery and the age of the parents are correlated factors. Among the internal factors are genetic factors, trisomy 21 and basilar invagination. Knowledge of these factors can contribute to the formation of screening, diagnosis, and early treatment policies.

Keywords: Craniosynostosis. Genetic Phenomena. Congenital Abnormalities.

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INTRODUCTION

The prenatal conditions experienced by the mother during pregnancy are a strong predictor of the perinatal characteristics of the neonate. Factors associated with genetics and epigenetics are milestones involved in the development of the conceptus and are related to possible neonatal alterations (1) (2).

In addition, during pregnancy, maternal lifestyle habits are of fundamental importance both for the regulation of adequate fetal development and growth, from another perspective, deleterious habits such as smoking, drug consumption or inadequate diets can corroborate growth deficits and significant changes in the conceptus that, in turn, lead to them for life (2).

Neonates develop a connective tissue membrane that connects the cranial bones and corroborate a heated growth of the brain in the first years of life, these membranes are called fontanelles. At about 8 to 18 months of age, the anterior fontanelle, also known as bregmatics, closes, while the posterior fontanelle, or lambdoid, can close in the first month of life. This closure occurs by chemical and cellular signaling in a type of intermembranous ossification (2).

As the embryological effect is present in all prenatal, gestational and postnatal conditions, changes related to bone formation are also included in possible malformations. Cranial malformations related to early closure of the fontanelles, not allowing adequate development and disposition of cranial anatomical elements, are called craniosynostosis (2) (1).

Brachycephaly is understood as a deformation of the cranial vault, within the group of craniosynostosis, in which there is a flattening of the posterior region of the skull due to an early closure of the posterior fontanelle, generating an increase in the laterolateral diameter of the head and an elevation, not always evident, of the posterosuperior pole of the skull (1) (3).

Thus, the present study is justified in an attempt to expand the data from the samples for more comprehensive analyses on brachycephaly and aims to correlate the existence of this craniosynostosis with her maternal gestational history.

METHODOLOGY

This is an integrative review in which a study of the literature is necessary to establish which parameters correlate with the guiding question. For the selection of

articles, 10 works were collected in the Google Scholar indexer in Portuguese, English and Spanish, and as an inclusion criterion the work would need an approach centered on the guiding question "what intrinsic and extrinsic factors could affect gestational development in order to occur craniosynostosis?", in addition to this, the works should necessarily deal with craniosynostosis "Brachycephalynosis", which is the central objective of the present work.

In addition, studies under the following conditions were excluded: studies that make causal comparisons with animal models and studies that failed to bring a possible causal factor to the guiding question.

Therefore, of the 10 studies read in their entirety to verify adequacy, only 8 fit the established parameters, and the results collected were added in an integrative manner in the discussion.

DISCUSSION

In view of the analytical reading of the cases, the causal factors were separated into two categories: the internal beginner factors and the external beginner factors. Internal or intrinsic factors are related to the individual with brachycephaly, while external or extrinsic factors are related to pregnancy and maternal lifestyle habits.

INTERNAL BEGINNER FACTORS

Among these factors, factors related to genetics are highlighted, whether they are genomic alterations or chromosomal alterations.

According to the study "Craniofacial changes and oral particularities in trisomy 21", among the clinical characteristics that the patient with this aneuploidy, known as Down Syndrome, can develop is brachycephaly. This alteration is due to the genetic alterations attributed to the excess chromosome 21 in the somatic cells of the carrier individual - which contributes to the alterations in fetal formations, including cranial ones. Therefore, the presence of this syndrome is characterized as a possible causal factor for brachycephaly (4).

According to the article "Prevalence of malformations associated with basilar invagination and its clinical manifestations", there is also a relationship between brachycephaly and basilar invagination (5). Basilar invagination is one of the most common craniocervical malformations and occurs due to a prolapse of the upper region

of the spine towards the cephalic basilar region. These components seem to be even more correlated with brachycephaly when related to Chiari Malformation, a condition in which there is congenital herniation of intracranial content through the foramen magnum to the cervical canal region (6).

Another condition associated with craniocephalic alterations was the mutation in the FGFR3 gene located on the short arm of chromosome 4, a gene responsible for the embryonic formation of the skull and limbs. Multiple mutations in various types of genotypes at this location have implications for the formation of skull bones and the synthesis of cap bones. Therefore, there is evidence that genetic factors contribute to craniosynostosis (7).

EXTERNAL BEGINNER FACTORS

Among these factors, factors related to maternal life habits, prenatal care, gestational status and childbirth stand out.

According to the study "Cranial morphology and the relationship with delivery time in neonates in a maternal and child ward at the university hospital of Western Paraná", it was observed that a shorter delivery time was correlated with higher rates of craniosynostosis in the patients analyzed. The article itself, however, confronts the data obtained with possible existing biases, given that, according to the literature cited by the authors, longer delivery time could be a risk factor for the development of this malformation. Thus, it is difficult to establish a clear causal parallel between the time of labor and cranial alterations, given that there are biases that hinder a correct analysis of this data (8).

Another data related to childbirth was published by Schaefer et al. (9). According to the published study, the surgical mode of delivery by cesarean section was the one with the highest number of neonates with cranial malformations, including brachycephaly. However, according to the proposed statistical analyses, it was not possible to establish a direct correlation between the mode of delivery and the presence of these craniosynostosis. Therefore, according to this study, the mode of delivery does not have a statistically significant relationship with the presence of craniosynostosis (9).

In addition, another important predictor within the prenatal context is the mother's lifestyle habits and their correlation with possible teratogenic effects on the conceptus. Smoking is an influential factor in several congenital malformations, as well as in the

emergence of intrapartum complications. This effect derives from substances with mutagenic potential in cigarettes that can overcome the transplacental barrier and establish a harmful effect on a correct embryonic development. In addition, substances such as nicotine act by deregulating the normal blood flow of pregnant women, promoting a placental circulatory deficit and favoring the risk of maternal-fetal complications (10) (2) (11).

Maternal smoking, according to the same study, is parallel to the appearance of craniosynostosis in neonates and with greater severity of the conditions in neuropsychomotor aspects a *posteriori* (10). However, the level of evidence of these correlations is still controversial, due to the precariousness of data for analysis (10).

In this context, maternal age is a biological and genetic factor that includes a risk factor for congenital anomalies when it is not within the normal range. According to the Ministry of Health (MH) (12), advanced maternal age is an important risk factor associated with higher rates of intrapartum complications, maternal-fetal mortality and genetic-phenotypic recurrences associated with older prefertilized oocytes and a higher rate of exposure of their genetic material to mutagenic inclement weather (13). Among these complications, one study identified a correlation between brachycephaly and the advanced age of the parents (1).

CONCLUSION

It is therefore concluded that there are several causal factors of craniosynostosis, including brachycephaly. Triggering factors can range from the individual's own characteristics such as molecular genetics, aneuploidies and associated congenital syndromes, to even triggering factors of responsibility for the mother-baby binomial: such as time of delivery, maternal age and smoking habit.

However, studies that attempt to establish these causal parallels lack a major correlation factor, given that the samples analyzed are small and there is a low prevalence of craniosynostosis in the general population, and for this, many biases are difficult to exclude.

From now on, understanding the possible triggering factors, even with these limitations, becomes important for the creation of screening, prevention, and treatment measures in health services around the world.

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