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Hypothesis: Is Dura Mater the True Culprit Behind Chiari 1 Malformations?

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Abstract: In this article, we discuss the theory that an error in dural development and/or signaling is responsible for the occurrence of Chiari 1 Malformations (CM1). Other widely accepted theories such as the premature closure of the spheno-occipital synchondrosis, or the paraxial mesodermal defect during embryogenesis are discussed, along with the most relevant evidence to substantiate our hypothesis.

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1. Introduction

Although recently there have been disagreements regarding the exact definition of Chiari 1 Malformations (CM1), most commonly it is described as a caudal herniation of the cerebellar tonsils through the foramen magnum [1]. It is the most frequent type of Chiari malformations, with an estimated occurrence of 1/1000 live births. A universally accepted definition among clinicians is currently lacking, since the malformation demonstrates inconsistency in clinical and radiological findings. The primary cause of this lies in the developing comprehension of the origins of CM1 [2].

2. Current Knowledge and Accepted Theories

The Chiari 1 Malformation may arise from genetic factors or as a consequence of various conditions, including craniosynostosis, rasopathies, craniocerebral disproportion, abnormalities in CSF circulation, platybasia, secondary neurulation defects, and bone metabolic disorders. Whole genome sequencing in a large patient cohort may improve understanding of the subject. Recent studies have concentrated on identifying CM1-associated variants by examining familial cases and de novo mutations via exome sequencing [3]. The review by Yan et al. examines three main categories of CM1 according to anatomical features and associates them with genetic lesions: posterior fossa-linked, macrocephaly-linked, and connective tissue disorder-linked CM1. Interestingly, some studies have reported variations in the genetic alerations between dura and blood of CM1 patients [4]. Lock et al. also claimed that the dura mater tissue likely influences cranial bone growth, potentially contributing to the etiology of Chiari Type I Malformation (CMI) and associated conditions; however, it remains largely inaccessible, and its gene expression has not been extensively investigated. Additional technologies and methodologies are required to further validate these specific findings.

In the study by Dagtekin et al., it was shown that the mean length of the basiocciput appeared markedly reduced in the CM1 group relative to the control group [5]. Additionally, the average length of the supraocciput was dramatically reduced, while the mean diameter of the foramen magnum was greatly increased in the CM1 group compared to the control group and dry skulls. As

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such, morphometric findings indicated that, in CM1, a hypoplastic occipital bone, likely resulting from a paraxial mesodermal defect of the parachordal plate, leads to overcrowding in the posterior cranial fossa, which houses the normally formed central nervous system structures. Nevertheless, based on this theorem, CM1 should likely be present and symptomatic at a much earlier age such as infancy or young childhood, whereas the majority of patients who are symptomatic are adults [6]. Infant cases of isolated CM1 are, however, scarce, whereas a greater proportion of children with the malformation are asymptomatic compared to adults. Therefore, the pathophysiology of CM1 may not be merely restricted to foetal development.

The second prominent theory stipulates that CM1 may arise from a premature closure of the spheno-occipital synchondrosis. This has been addressed and investigated by Hwang et al., who found that several metrics were modified in CM1 patients compared to healthy controls, including a shorter clivus length, larger mean vertical height of the cerebellar hemispheres but a shorter anterioposterior axial diameter [7]. The modifications of the occipital bone lead to its funnel shape in CM1, the authors suggesting that the adequate cephalocaudal extension of the craniectomy in the posterior cranial fossa provides a greater decompression effect compared to other types of craniectomy extensions in these patients. Taken together, these two main theories converge on an improperly formed occipital bone. The issue of the dura mater lining the posterior fossa as the primary (or even singular) culprit of this malformation has, to the best of our knowledge, not yet been addressed.

3. The Dural Connection

The occipital bone is formed through both intramembranous and endochondral ossification via six separate ossification centers, namely the basioccipital bone, two exoccipital bones, one supraoccipital bone, and two interparietal bones [8]. Intramembranous ossification involves the transformation of connective tissue membranes into osseous tissue, while endochondral ossification pertains to the conversion of hyaline cartilage into osseous tissue. The occipital plane, a component of the squamous occipital bone, develops by the intramembranous ossification process, whereas the rest of the occipital bone grows through endochondral ossification.

Comprehensive morphometric data about the progression of ossification centers in human fetuses may facilitate the early identification of developmental anomalies. Comprehending the growth and development of the occipital bone is essential for evaluating the normal and pathological development of the cranial base. Abnormalities in the development of the occipital bone may include stenosis of the foramen magnum in thanatophoric dysplasia, deformities associated with anencephaly, or the shallowing of the posterior cerebral fossa characteristic of Chiari malformation [9]. Also according to Grzonkowska et al., in developing human fetuses the morphometric features of the major ossification centers of the lateral and basilar regions of the occipital bone exhibit no variations related to sex or laterality. The principal ossification centers expand linearly in relation to their sagittal and transverse diameters, surface area, and volume. However, as of yet, quantitative studies of primary ossification centers in the skull using computed tomography (CT) have rarely been conducted due to the scarcity of fetal human specimens, as well as the concerns regarding fetal exposure to ionizing radiation. Moreover, prospective data may be difficult to obtain, as it would require a wide pool of subjects to perform repeat cranial imaging studies during a long timeframe.

The dura mater plays a crucial role in the ossification and formation of the inner table of each flat bone of the cranial vault [10]. As the normal brain expands, the calvarial bones are displaced outward, also partially due to the increasing meninges. As the bones are separated by their displacement motions, the osteogenic sutural membranes generate membranous bone in quantities commensurate with the degree of displacement, thereby increasing the circumference of each bone and maintaining continuous articular contact. Bone size can increase by deposits along the margins next to sutures. The periosteum contributes to the increase in thickness and size of the bone by intramembranous ossification on the outer surface. Concurrently, bone is excised from the inner surface. Consequently, when the bone enlarges, the cranial cavity concurrently expands.

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4. The Hypothesis

The stimulation of bone growth originates mostly from the enlarging brain, though not by directly exerting physical pressure. Rather, this process is indirect, the brain transmitting impulses via the dura mater [10]. As the brain enlarges and the cranial base synchondroses extend, the sutures compensate by adding intramembranous bone at the peripheries of the bone fronts, thereby maintaining a relatively constant width of the sutures while the cranial vault expands to accommodate the growing brain. If this holds true, then the growth of the dura mater is intrinsically linked to the develpment of the bone, while the expanding brain is dependent on the proper function of the dura mater for its accomodation in the posterior fossa. An interruption in the signalling between the dura mater and the bone, or an arrest in the normal osteogenic function of the dura mater, may be the actual key in the appearance of CM1.

Considering our hypothesis that the dura plays a primary role in hindering occipital bone growth, we believe that aside from the sufficient cephalocaudal extension of the craniectomy, a durotomy may also be warranted, as the dura itself also adopts a funnel shape and is rigid. Recently, we have published a technical note on our approach to CM1, the interlayer dural split technique, which is a less invasive method of increasing the overall size of the dura mater at the posterior fossa, without the risk of CSF fistula as we only incise the outer dural layer [11]. As such, we allow the inner layer to expand and better accommodate the contents of the posterior fossa. Dural stripping has also been described, though its results are rather discouraging according to some [12].

5. Concluding Remarks

In conclusion, we postulate that this alteration in the growth of the occipital bone may not be entirely due to foetal developmental anomalies, but rather a primarily postnatal arrest in normal dural growth and ossification signalling. It remains to be seen whether this theory will be confirmed or disproven, however a prospective craniometric analysis by means of repeat high-resolution imaging may seem unfeasible at this time. Genetic studies might provide the best evidence to substantiate this theory. This letter is should be viewed as a call for researchers in the fields of embryology, genetics, pathophysiology, and neurological development as well as neurosurgeons to definitively elucidate the etiological mechanism of CM1.

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