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Original Article

A morphometric assessment of type I Chiari malformation above the McRae line: A retrospective case-control study in 302 adult female subjects

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Purpose. – Type I Chiari malformation (CMI) is a radiologically-defined structural dysmorphism of the hindbrain and posterior cranial fossa (PCF). Traditional radiographic identification of CMI relies on the measurement of the cerebellar tonsils in relation to the foramen magnum with or without associated abnormalities of the neuraxis. The primary goal of this retrospective study was to comprehensively assess morphometric parameters above the McRea line in a group of female CMI patients and normal controls.
Material and methods. – Twenty-nine morphological measurements were taken on 302 mid-sagittal MR images of adult female CMI patients ($n = 162$) and healthy controls ($n = 140$). All MR images were voluntarily provided by CMI subjects through an online database and control participant images were obtained through the Human Connectome Project and a local hospital system.
Results. – Analyses were performed on the full dataset of adult female MR images and a restricted dataset of 229 participants that were equated for age, race, and body mass index. Eighteen group differences were identified in the PCF area that we grouped into three clusters; PCF structures heights, clivus angulation, and odontoid process irregularity. Fourteen group differences persisted after equating our CMI and control groups on demographic characteristics.
Conclusion. – PCF structures reliably differ in adult female CMI patients relative to healthy controls. These differences reflect structural abnormalities in the osseous and soft tissue structures of the clivus, odontoid process, and cerebellum. Clinical and pathophysiological implications are discussed.

Introduction

Radiographic characterization of Chiari malformation I (CMI) is typically determined by a tonsillar position (TP) below the foramen magnum (FM) greater than three to five millimeters [1,2]. Most estimates approximate CMI prevalence as 0.1%, though estimates vary considerably as a result of variable diagnosis criteria, with symptomatic CMI often remaining entangled with asymptomatic tonsillar ectopia, which presents with much greater frequency [3–7]. Structurally, several aspects of CMI have been suggested to differ from healthy individuals apart from the cerebellar TP, often referred to as descent or herniation, albeit with conflicting conclusions on which measurements are most useful in clinical and research environments. Furthermore, the degree of descent in CMI is nominally informative of patient symptomatology and long-term consequences [4,8]. Thus, it is valuable to identify additional morphometric parameters of CMI, particularly those that can better inform clinical diagnosis and prognosis as well as pathophysiology.

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The goal of this study is to present a comprehensive comparison of structural parameters of brain and cranial morphology that can be identified from mid-sagittal magnetic resonance (MR) images between CMI patients and healthy controls.

Many studies have suggested morphological markers other than TP that are different in CMI patients and healthy controls, which in the long run, may help differentiate CMI patients with varying degrees of symptomatology. Milhorat et al. posited that a smaller posterior cranial fossa (PCF) is the principal attribute of CMI [1]. While this hypothesis gained support in subsequent investigations of structural MR imaging [9–15], others found no association between PCF area and CMI [8,16,17]. Moreover, multiple studies have led to the discovery of a limited association between PCF morphology and TP within an individual [11,18–21], suggesting that the PCF may provide unique indication of CMI status apart from TP.

Related to the interest in PCF morphology as an etiologic factor in the development of CMI, there has also been considerable interest in the occipital bone as well as basilar invagination of the odontoid process. For example, the retrograde angulation of the odontoid process, a common presentation of CMI, is thought to compromise the PCF [11,13,22,23]. Beyond PCF, occipital and odontoid morphology, other research efforts have explored the relationship of platybasia (flattening of the skull base), clivus underdevelopment, tentorial angulation, oropharynx anomalies, and other PCF and cerebral abnormalities with CMI diagnosis [9–11,13,14,19,24–28].

Given the growing body of evidence supporting the notion of additional structural markers of CMI beyond TP above the McRae line, it is important to acknowledge that the consistency of these morphological effects remains elusive. For example, several authors have reported shorter clivus lengths in CMI patients [1,9,10,12,13,15,16,24,28–30]. Yet, others have found no differences between CMI patients and healthy control participants [11,19]. Similar patterns of discordant findings are apparent for other structures in the PCF. In part, these inconsistencies may be explained by the limitations of participant sample sizes and the uniformity of the CMI patient groups used to identify morphologic associations. Roller et al. recently brought this confound into discussion on their investigation of morphological differences in 162 CMI, idiopathic intracranial (IC) hypertension, and healthy controls [31]. The researchers determined that, in their sample, sex, ethnic background, and BMI were all associated with measures of the PCF and IC cavity (also see [22] for a discussion of gender dependent odontoid morphology). Furthermore, after controlling for the demographic variables, the researchers found no significant association between CMI status and cerebellar, cerebral, or bone morphometry. The authors argued that the observation of this null effect after applying stricter inclusionary criteria potentially explains the inconclusive results on brain morphometry.

It is also possible that the lack of convergent findings stemmed from the relatively small sample sizes often typical of CMI morphometric investigations, allowing for sampling error to contribute to the uncertainty of reported effects. Thus, large-scale studies with CMI and control participants balanced in demographic characteristics are needed to separate disparate findings from those that deserve further investigation. The current study aimed to provide a series of cerebral, cerebellar, and osseous structures of the skull base and PCF using a relatively large sample of adult female CMI patients and control participants. In addition, a reduced sample was examined that was balanced for age, ethnic background, and body mass index (BMI). With this sample reduction, along with the exclusion of male participants to control for sex-dependent morphological differences [22], it was possible to address demographic influences on morphological differences between adult CMI patients and control participants.

Methods

Institutional review approval

This study was submitted and approved by the local institutional review board of the University of Akron and Akron General Medical Center (approval #201504145 and 14018, respectively).

Participants

Pre-surgery MR images of 302 adult females, 162 with CMI and 140 healthy controls, were evaluated for this study. CMI patients were considered for the study contingent upon reporting to have received a diagnosis by a physician. Demographic data, health-related data, and MR scans were voluntarily provided by CMI subjects through the Chiari1000 project with consent for anonymized use in scientific investigations. The Chiari1000 project, a web-accessed database, was established at The University of Akron in 2015 to collect and store data on the diagnosis, symptomatology, cognitive, and socio-emotional characteristics of CMI patients as well as their medical images (MR, computed tomography, ultrasound, etc.). Patients volunteered images through direct mail, online sharing (e.g. Dropbox), or signing a release to allow acquisition of images from their healthcare center. Among the participants, 47.9% reported having underwent a surgical procedure related to their malformation. Pre-surgery status was determined by patient disclosure, surgical records when available, and visual inspection. In the circumstance that pre-surgery status could not be confirmed, the patient was excluded from analysis. Male MR images were excluded due to poor representation in the database at the time of analysis. De-identified MR images were stored on an OsiriX DICOM PACS server (Pixmeo SARL, Geneva, Switzerland) at The University of Akron. Demographic information and MR images of healthy female control subjects were obtained through the Washington University, University of Minnesota, and Oxford University Human Connectome Project consortium [32] and supplemented by images acquired locally through the Akron General Medical Center. Control participants did not have any conditions known to affect brain morphology and were free of illness.

MR image selection and evaluation

MR images of the participants of the study were reviewed. The studies received were performed either on 1.5 T or 3 T scanners. Scans were performed on magnets from the following vendors: General Electric (Fairfield, CT), Philips (Amsterdam, Netherlands), Siemens (Munich, Germany), and Toshiba (Minato, Tokyo, Japan).

Mid-sagittal pre-surgical T1- ($n = 297$) and T2-weighted ($n = 5$) MR images were assessed and included in the study. Measurements were carried out on an operator-selected mid-sagittal image for each participant. Image resolution was key in making the measurements, and images were rejected if image quality did not meet mid-sagittal selection criteria. Criteria for mid-sagittal selection consisted of the visibility of at least three of four structures in a single sagittal image:

- the genu of the corpus callosum;
- the splenium of the corpus callosum;
- the pituitary infundibulum;
- the cerebral aqueduct.

Measurement software

Twenty-nine parameters were obtained from the PCF compartment, craniocervical junction, oral cavity, and IC structures using linear, angular, and area measurements (Fig. 1). Structures were