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Determining if a Relationship Exists Between Tonsillar Ectopia and Symptom Presentation in Chiari Malformation Patients

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Purpose

Chiari Malformation Type I (CM I) is characterized by cerebellar tonsil ectopia and has varying symptomatology. Previous research has shown a relationship between tonsillar dominance and related conditions but few examined association with symptomatology. This study attempts to elucidate a relationship between cerebellar tonsil dominance, age, and symptomatology.

Methods

Data from CM I patients were extracted from the *Conquer Chiari Patient Registry*. Tonsillar dominance was determined using a ratio of right-to-left herniation length. Pearson's correlation and one-tailed Student's T-test were used for analysis.

Results

Length of tonsillar descent appears to be negatively correlated to age of onset ($r = -0.266$; $p < 0.001$; $n = 113$) and diagnosis ($r = -0.323$; $p < 0.001$; $n = 113$). No correlation was found between tonsillar dominance and symptom location, nor between tonsillar dominance and symptom severity bilaterally ($p > 0.05$). Symptom location and severity ratios appear to be correlated ($r = 0.666$; $p < 0.001$). Tonsillar descent length appears to be strongly correlated bilaterally ($r = 0.972$; $p < 0.001$; $n = 50$).

Conclusion

Inconsistency between tonsillar dominance as related to symptomatology suggests a multifactorial contribution to clinical presentation. The inverse relationship between tonsillar herniation length and age of symptom onset and diagnosis suggests herniation length may be an important predictor for clinical outcomes. Further research is needed to elucidate additional contributing factors and tonsillar dominance and symptomatology association.

Abstract

Chiari malformation type I (CM I) is a disorder in which the cerebellar tonsils descend caudally through the foramen magnum¹. While there are discrepancies in current literature, it is conventionally acknowledged that the tonsillar descent must be at a minimum of 3-5 mm, as shown on diagnostic radiographic images, in order to diagnose CM I. There are several hypotheses as to why CM I occurs including genetic and ethnic factors, an increase in intracranial pressure or a decrease in intracranial volume, all of which may contribute to a malformation of local neural structures². Symptomatic manifestations of CM I are associated with a tonsillar herniation of greater than 12 mm in accompaniment to findings of molded cerebellar tonsils and reduced space for cerebrospinal fluid flow in the tonsillar area². Symptoms may be present with shorter herniation², prompting research into the relationship between tonsillar descent and symptom severity. This research seeks to examine two relationships. First, patient-reported data was analyzed to determine if a potential relationship exists between right-versus left-sided lateral predominance of cerebellar tonsillar descent in CM I and symptom presentation. Second, the study seeks to determine if a similar relationship exists between tonsillar ectopia dominance and the asymmetry of clinical manifestations in the same patient-reported sample. To our knowledge this is the first study that is based upon patient-reported data exploring if such relationships exist. Our study did not find a significant relationship between tonsillar dominance and symptom presentation. The lack of correlation between tonsillar herniation dominance and symptom presentation, as would be expected from neuroanatomic relationships, suggests a multifactorial cause for individual symptomatology and warrants further investigation.

Introduction

Chiari Malformation (CM) is a complex disorder of poorly understood etiology but has a classification scale of type I-type IV. Type I (CM I), is often diagnosed in adulthood and precipitated by head trauma. Type II (CM II), is more commonly diagnosed in childhood and associated with other congenital anomalies such as tethered cord³. Types III and IV of CM exist but will not be discussed in this manuscript. For CM I, tonsillar herniation is defined as herniation of the cerebellar tonsils through the foramen magnum by 5 mm or more. By convention, T1weighted sagittal MRI scans is used to quantify the degree of ectopia, and tonsillar herniation is measured from the tips of the cerebellar tonsils to a line drawn between the basion and the opisthion³. It should be noted that CM is one of many posterior fossa abnormalities, including Dandy-Walker malformation, and investigation with MRI is necessary for accurate diagnosis and treatment. Multiple anomalies can occur together, such as tonsillar ectopia with concomitant compression of the cerebellar cisterns and empty sella syndrome, though the etiology behind such a relationship has yet to be elucidated³.

Previous research by the authors showed the mean age of symptom onset for a national sample of 768 individuals with CM I, to be 20.7 years of age (SD = 13.7) with mostly women being affected (80.4%)¹³. In addition, the preponderance of respondents 92.7% were Caucasian. Milhorat *et al.* described a similar demographic, with age of onset being 25.2 (SD = 14.2) with a female predominance of 94% (n = 126)³. An exact prevalence of CM I has yet to be established¹⁵, but it is estimated that 215,000 Americans suffer from CM I, although this number is believed to be an underrepresentation¹⁶. Such underrepresentation exasperates gender, age, and race/ethnicity disparities making prevalence estimates inaccurate

Much is still unknown about CM I presentation because of the range of symptoms patients experience such as headaches, vestibular abnormalities, and ophthalmological disturbances,³ while other patients present with fewer symptoms. For some affected individuals, the descent of the cerebellar tonsils may not be of equal length bilaterally. Little research exists as to the relationship of asymmetric tonsillar descent and symptom characterization based on severity and location. Previous research by Deng et al.⁴ has shown a correlation between tonsillar ectopia dominance and syrinx location, the ratio of tonsillar descent to the ratio of syrinx deviation, and tonsillar ectopia dominance and syrinx location in relation to scoliotic curvature. Research by Tubbs *et. al*⁵ found that asymmetrical tonsillar descent in CM I may suggest an asymmetrical cervicomedullary compression and further clinical implications. With a variety of definitions and symptom presentation, further research is necessary to confirm such suggestions.

Lack of a relationship between tonsillar dominance and symptom presentation may also be due to the complexity of information relay pathways from the body to higher brain centers.

Somatosensation of vibration, pressure, and discriminative touch, for example, is relayed through the dorsal column medial lemniscus (DCML) system, such that the right brain perceives somatosensation of the left side of the body². For this reason, right-sided tonsillar compression at the level of the medulla where the medial lemniscus is present may cause numbness in the left side of the body, whereas compression below the decussation may result in numbness on the right side of the body. For purposes of this research dominance refers to left- and right-brain tonsillar ectopia and symptom presentation.

In addition to the DCML system, the anterolateral system portion of the nervous system is of importance in relaying information about temperature, pain, and crude touch to higher centers in the brain. Information regarding these sensations is transmitted by the ascending anterior and

lateral spinothalamic tracts. Similar to the DCML system, these tracts within the spine ascend ipsilaterally, synapsing with second-order neurons which then decussate to the contralateral side via the anterior white commissure. The anterolateral system then projects to the thalamus to provide an individual with sensation of crude touch, pain, and temperature. Due to the decussation of the anterolateral system, damage could potentially cause ipsilateral or contralateral deficit from anesthesia. These deficits would be presented contralaterally if a lesion were rostral to the decussation, and ipsilaterally if a lesion were caudal to the decussation². Thus it is possible for a patient to be either unable to sense pain and temperature if the anterolateral system is damaged, or unable to sense vibration and fine touch if the DCML system is damaged². However, this specific information regarding deficits in those with CM I, which would be tested during a neurological examination, was not available from this survey. Future studies analyzing the relationship between tonsillar dominance and symptom presentation should consider herniation position along the DCML system and anterolateral system, to more accurately elucidate trends.

Methods

The United States-based Conquer Chiari Research Center and Conquer Chiari Research Foundation established a voluntary, dynamic, online *Conquer Chiari Patient Registry* for individuals with CM and caretakers. Participants were made aware of the registry by advertisements through the foundation's websites (conquerchiari.org, chiari-research.org) and CM message boards. Information regarding clinical presentation, diagnostic experience, and quality of life was collected. Survey components were completed from the launch date, August 2012, until April 2014 when data was collected for analysis. Survey participants were required to have a diagnosis of CM via a physician or diagnostic MRI consisting of a tonsillar ectopia of

greater than 5 millimeters. They also must be at least age eighteen, although parents and legal guardians may enter data into the registry for patients under the age of eighteen with CM.

Participants were not compensated and their information was de-identified. As of April 2014, 957 individual participants provided responses to survey-style questions. Participants also had the choice to skip over questions as is evident with this research (further defined below). This registry signifies the first time that individuals living with CM can self-report about their experiences.

Instruments

Survey participants were asked if they had access to MRI reports and subsequently prompted to enter information about MRI findings, including length of tonsillar descent (in mm). Patients who did not indicate having access to an MRI report were not included in this study. Patients also provide responses to a vast array of questions regarding type, location, and intensity of CM I symptoms. Zhu's method for calculating the asymmetry of tonsillar descent (hereafter referred to as tonsillar length ratio) was used⁶. The measure of right tonsillar descent was divided by the measure of left tonsillar descent. Similar to Deng et al.⁴, we considered a tonsillar length ratio greater than 1.10 and less than 0.90 to represent right and left dominance, respectively. Tonsillar length ratio values that fell between 0.90 and 1.10 were considered to be symmetrical.

Cerebellar tonsil descent was compared to the severity of symptoms as reported by the patient (mild, moderate, severe, very severe) and localized to the right or left side. Symptoms were localized to the arm, hand, leg, and foot bilaterally. Since symptom asymmetry could not be evaluated in a clinical setting, frequencies of right and left symptom presentation were calculated by assigning binary values to "yes" and "no" reporting of symptoms along the extremities for

each side of the body. For example, an individual who reported numbness and tingling along the right hand, right arm, and right leg with only symptom presentation on the left localized to the hand would receive a score of 3 for the right and 1 for the left (see *Figure 1: Symptom Scoring Schematic*). A symptom localization ratio was performed as with the tonsils, dividing the summed symptoms for the right side by the summed symptoms for the left. Similar to tonsillar length, we considered a symptom localization ratio greater than 1.10 and less than 0.90 to represent right and left dominance, respectively. Symptom localization ratio values that fell between 0.90 and 1.10 were considered to be symmetrical. For the previous example, the individual would be considered right-dominant concerning symptom presentation.

Statistics

Data were extracted from the dynamic, online *Conquer Chiari Patient Registry* and imported into SPSS version 22 (IBM/SPSS, Inc., Chicago, IL). Pearson's correlation and one-tailed Student's t-test were used to analyze the relationship of side dominance between tonsillar herniation and clinical presentations. Pearson's correlation and one-tailed Student's t-test were also performed to analyze the correlation between tonsillar herniation distances and symptom severity. An alpha of 0.05 was set with significance of $p < 0.05$.

Results

Tonsillar Asymmetry and Clinical Manifestation

Patient data was included if the following criteria were met: 1) the individual inputting data was a patient or the parent of a patient, 2) the individual inputting data had access to an MRI and 3) the patient was diagnosed by a physician or MRI to have CM I. The sample size decreased from 786 to 316 individuals (*Figure 1*).

Table 1 details patient demographic information. The majority of our sample identified as female (80.4%) and Caucasian (92.7%) with mean age of 34.9 (SD 15.0) years. Average age of symptom onset was 20.6 (SD 13.9) years with average age at diagnosis of 32.5 (SD 15.7) years.

As seen in *Table 2*, tonsillar descent ranged from 0 to 35 mm on the right side (mean 9.30 mm; SD 5.90 mm), and from 1 to 35 mm on the left side (mean 9.52mm; SD 5.78 mm) with the overall tonsillar herniation range from 2 to 29 mm (mean 9.43 mm; SD 5.06 mm). Right-sided tonsillar dominance was present in 10 (14.1%) individuals with left-sided dominance present in 13 (18.3%) of individuals and overall symmetry present in 48 (67.6%) of individuals. Length of tonsillar descent (mm) appeared to be negatively correlated ($r = -0.266$; $p < 0.001$; 95% C.I. - 0.429 to -0.086) to age of onset (years) and age at diagnosis ($r = -0.323$; $p < 0.001$; 95% C.I. - 0.479 to -0.148) for 113 individuals.

Patients were then excluded from further analysis if they had undergone surgery or had been diagnosed with a disease, such as multiple sclerosis, which may account for muscle weakness, numbness, or tingling, so as not to skew statistical results involving symptomatology. The new sample size was further reduced to 273 individuals (*Figure 1*).

Clinical manifestations were localized to the right ($n = 117$; 52.2%) or left ($n = 51$; 22.8%) side or were equally represented ($n = 56$; 25.0%) on both sides of the body (missing data: $n = 49$). Symptom severity was also localized to the right ($n = 40$; 22.3%) or left ($n = 46$; 25.7%) side or were symmetrical ($n = 93$; 52%) over the body (missing data: $n = 94$). Symptoms included in the analysis were numbness, tingling and weakness located in the left or right arm, hand, leg, and foot. Multiple imputations were considered for the missing data; however, due to the structure of

the survey it is difficult to determine if patients did not know the answers or were just electing not to respond.

Tonsillar Descent and Symptomatology

Pearson's correlation and one-tailed Student's t-test ($\alpha = 0.05$) were used to compare dominance of tonsillar descent, symptom severity, symptom location, and symptom presentation. A one-tailed t-test was used because our study was only interested in tonsillar descent through the foramen magnum and not tonsillar regression. For this reason, a one-tailed t-test allowed for greater statistical power in detecting significant differences along one side of the Gaussian curve. No correlation was found between tonsillar dominance and symptom location ($r = 0.028$; $p = 0.426$), nor between tonsillar dominance and symptom severity localized to the right or left side of the body ($r = 0.98$; $p = 0.301$). However, symptom location and severity ratios were correlated ($r = 0.666$; $p < 0.001$), indicating a positive relationship of association between the symptom and patient report of severity of symptom. Cerebellar tonsil descent length was strongly correlated bilaterally ($r = 0.972$; $p < 0.001$; $n = 50$), with the descent length related to symptom location.

Tonsil herniation (mm) and patient self-report of symptom severity produced strong associative relationships. Right tonsillar herniation length appears to be correlated with right symptom presentation ($r = -0.531$; $p = 0.001$; $n = 32$; 95% C.I. -0.742 to -0.224) and symptom severity localized to the right side of the body ($r = -0.534$; $p = 0.001$; $n = 31$; 95% C.I. -0.746 to -0.222). Left tonsillar herniation length appears to be negatively correlated with right symptom presentation ($r = -0.489$; $p = 0.002$; $n = 3$; 95% C.I. -0.709 to -0.181) and symptom severity localized to the right side of the body ($r = -0.504$; $p = 0.001$; $n = 33$; 95% C.I. -0.722 to -0.195).

A similar relationship involving tonsil herniation and symptomatology was not seen involving the left side of the body. Individual localized symptoms (e.g., pain in the right hand) were also compared to tonsillar dominance, but a relationship between these variables was not observed ($p > 0.05$).

Discussion

The results of our study further emphasize that much is left to be understood about CM I, including a better understanding of etiology and the impact of tonsillar compression of the brainstem and spinal cord, especially concerning symptom presentation and correlation. Establishing relationships between tonsillar descent and symptomatology may allow for predictions of symptomatology or patient morbidity. The lack of correlation between tonsillar herniation dominance and symptom presentation, as would be expected from neuroanatomic relationships, suggests a multifactorial cause for individual symptomatology. Knowing the implications of tonsillar descent length and dominance will further our understanding of CM I as a whole and possibly help tailor treatment options to patients predicted to exhibit certain symptoms or symptom severity. Our study attempted to elucidate relationships involving tonsillar dominance, symptom presentation and severity. While previous studies have described tonsillar asymmetry with respect to related conditions, to our knowledge, this is the first time symptom presentation dominance and severities were analyzed in relation to tonsillar dominance^{4,7}.

Our patient sample largely reflects that of previous studies, with higher representation of females (80.4%) than males^{3,8-10}. It is impossible to know if our large proportion of Caucasian (92.7%) patients is representative of those affected with CM due to underrepresentation of minorities in

research⁸ and the lack of inclusion of racial and ethnic information in previous Chiari studies^{3,8-10}. For this study, we were not able to determine why there is such a disparity in our sample.

A majority of individuals showed tonsillar asymmetry in clinical research by Zhu et al.⁷ (87%; n individuals = 39) and Deng et al.⁴ (91.3%; n individuals = 104), however our study based on patient reporting indicated symmetry as being more common (67.6%; n = 71). Smith et al.¹¹ also showed symmetry in 84% of cases and much larger sample size (n individuals = 2400).

Disproportionate cranial and cerebral dimensions were thought to be related to Chiari onset and symptomatology, with CM II being diagnosed as a congenital form and CM I being acquired after trauma¹². However, a relationship was not found with regard to tonsillar descent¹². Clinical manifestations and severity, therefore, may not be predicted solely by cranial and cerebral architecture. Our study attempted to elucidate a relationship between tonsillar ectopia and symptomatology. Possible negative correlations were observed bilaterally with symptoms localized to the right side of the body. However, a similar relationship was not observed for the left side, highlighting a lack of consistency between variables.

Anomalies concerning association between tonsillar eccentricity and related conditions are not unique to the current study⁷. Zhu et al.⁷ explains that various imaging techniques may account for alternate findings between studies, a problem which appears to be exacerbated in smaller sample sizes. This survey does not provide specific information on the characteristics of the MRI being viewed, to determine the length of the patient's cerebellar tonsils. There is also clinical inconsistency as to what criteria necessitate CM I diagnosis.

Symmetrical symptom presentation is more easily explained, especially in individuals showing symmetrical tonsillar ectopia. Symptoms may also present symmetrically in those expressing

tonsillar dominance, either by causing bilateral compression of the brainstem as the unaffected side is forced against bony architecture, or simply by compressing along the length of nerve projection pathways, involving both the contralateral (more rostral) and ipsilateral (more caudal) portions of the same pathway.

It is interesting that symptom severity was reduced as tonsillar herniation length increased, despite the fact that a larger area of the brainstem and spinal cord would be compressed. Patients suffering from CM I may also present with morphological changes to the tonsils themselves, such as cone-shaped elongation as the tonsils herniate through the foramen magnum¹⁰.

Elongation in this way may cause tapering of the tonsils, and this reduction in thickness could possibly result in reduced compression over the length of descent and subsequent reduction in symptom presentation. Further research is warranted to determine if such a phenomenon occurs.

The importance of early intervention has been established in improving clinical outcomes¹³ and patient quality of life^{13,14}. Intervention delay is associated with increased risk of developing debilitating symptoms such as ataxia, vertigo, and severe headache syndrome⁸. The inverse relationship between tonsillar descent length and age of onset and diagnosis suggests severity of herniation may be an important predictor of clinical outcomes.

This study is the first time that symptom localization and severity are compared to tonsillar dominance. The data for this study was collected from the online *Conquer Chiari Patient Registry* (CCPR). The voluntary, self-reporting nature of the CCPR allows for great insight into the impact of CM I on many individuals. However, the survey did not require that individuals complete every question, resulting in incomplete data entry and missing data. We were unable to access individual MRI reports to determine if imaging was consistent between patients, nor were

we able to determine tonsil position in relation to the brainstem and spinal cord to better ascertain which neural structures might be compressed. Further research is needed to examine if a relationship between tonsillar dominance and symptomatology in a larger sample size exists in order to reveal possible trends.

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Conflict(s) of Interest None.

Ethical Standards The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation as approved by the Institutional Review Board at The University of Akron and Northeast Ohio Medical University and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1: Demographic Information

	No. CM I	% CM I (n = 316)
Gender		
Female	254	80.4
Male	49	15.5
Missing	13	4.1
Race*		
White or White-Hispanic	293	92.7
American Indian	10	3.2
Black, African American, or Black Hispanic	7	2.2
Asian	3	0.9
Other	5	1.6
Age (mean(SD)) years	34.9 (15.0)	-
Age at Symptom Onset (mean(SD)) years	20.6 (13.9)	-
Age at Diagnosis (mean(SD)) years	32.5 (15.7)	-

*Individuals were able to identify with more than one race but the total number of individuals who answered remained n = 316.

Table 2: Clinical Presentation

	No. CM I	% CM I
Tonsil Herniation (mean(SD)) mm (n = 316)		
Right	9.30 (5.90)	-
Left	9.52 (5.78)	-
Symmetrical	9.43 (5.06)	-
Tonsillar Dominance (n = 71)*		
Right	10	14.1
Left	13	18.3
Symmetrical	48	67.6
Missing	245	-
Symptom Dominance (n = 224)*		
Right	117	52.2
Left	51	22.8
Symmetrical	56	25
Missing	49	-
Symptom Severity Dominance (n = 179)*		
Right	40	22.3
Left	46	25.7
Symmetrical	93	52.0
Missing	94	-

*Percentages and sample size do not include missing data.

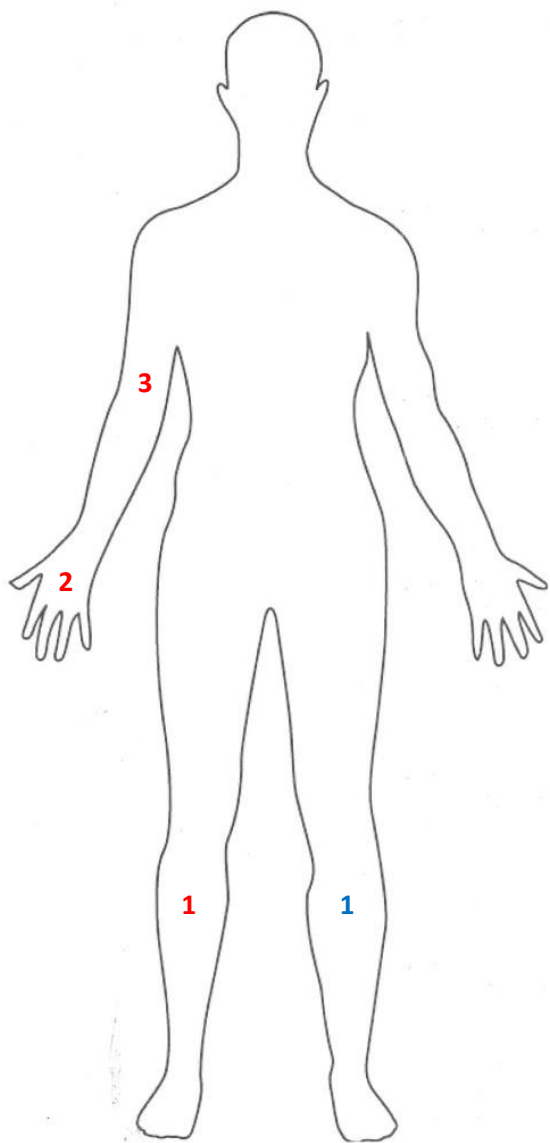


Figure 1: Symptom Scoring Schematic

Figure 2: Tonsillar Ectopia Patient Selection

