Familial Chiari Malformation: A Systematic Review

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BACKGROUND

- Chiari Malformations (CM0-IV) are a rare group of congenital or acquired brain disorders characterized by hindbrain overcrowding into an underdeveloped posterior cranial fossa.[1]
  - This causes the cerebellar tonsils to herniate through the foramen magnum into the spinal canal with a descent of ≥ 5mm.[2]
- CM1 is considered largely sporadic; however, strong evidence of its genetic underpinnings exist due to increasing CM familial aggregation case reports, twin studies, CM cosegregation with known genetic conditions, and recent genome-wide studies.[3]
- **Objectives:** (1) investigate a genetic component to CM; (2) identify CM symptom and co-morbidity patterns; (3) provide recommendations to monitor at-risk family members.

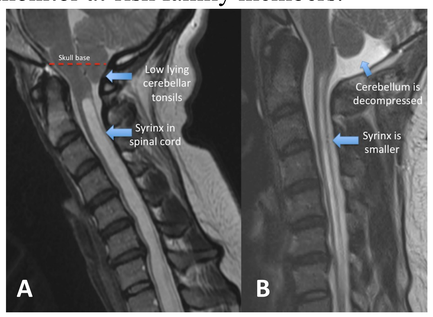

Figure 1: *(A) CM1 before intervention; (B) CM1 following decompression surgery[4]*

METHODS

- The EMBASE and MEDLINE databases were searched in May, 2022 with the key terms: "*Chiari malformation AND family*", "*Chiari malformation AND siblings*", "*Chiari malformation AND twins*", "*Chiari malformation AND parents*".
- Inclusion criteria: English, CM diagnosis in >1 human family member presented as a case study, case series, or literature review.
- **Final analysis:** 27 articles, 31 different families, 89 total cases.
  - Patient clinical details (medical history, CM symptoms, tonsillar herniation, associated syringomyelia), familial relationship, and outcome of surgical/non-surgical intervention were extracted from each case to create a literature review table.

RESULTS

- **Average span of generations:** 2 (range: 1-4)
- **Average age:** 24 yo (± 16)
- **Average tonsillar descent:** 8.89 mm (± 4.4) using entire sample
  - CM + syrinx: 10.3 mm (± 5.0) in 15 patients
  - CM w/o syrinx: 9.3 mm (± 3.0) in 12 patients ($p > 0.05$)
- **Syrinx prevalence:** 34 (38%) cases, with 15 (44%) of these patients also reporting a skeletal disorder.

Table 1: *Symptom Distribution (n = 89 cases)*

Symptom Category	Symptom Frequency (%)
Generalized Symptoms	32 (36%)
Sensory Disturbances	22 (25%)
Visual Disturbances	18 (20%)
Upper Motor Neuron Deficits	16 (18%)
Otoneurologic Disturbances	13 (15%)
Ataxic Movements	11 (12%)
Sleep Disturbances	7 (8%)
Bulbar Disturbances	5 (6%)
Lower Motor Neuron Deficits	5 (6%)
Bladder/Bowel Symptoms	4 (4%)
Joint Involvement	3 (3%)

Table 2: *Medical History Distribution (n = 89 cases)*

Comorbidity Category	Condition Frequency (%)
Skeletal abnormalities	28 (31%)
Other	13 (15%)
Obstetric complications	9 (10%)
Endocrinopathies	6 (7%)
Cranial abnormalities	5 (6%)
Cardiovascular and respiratory	5 (6%)
Movement/muscle disorders	5 (6%)
Neuropsychiatric	4 (4%)

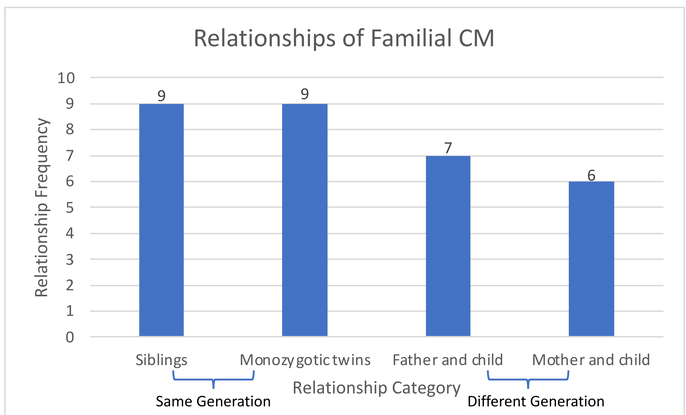

Figure 2: *Relationship of Familial Chiari (n = 31 families)*

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DISCUSSION

- Most of the posterior fossa morphology is heritable, influenced by genes affecting mesoderm development, posterior fossa volume, cerebral tonsil herniation, and syrinx formation.[5]
- It is suggested that CM inheritance can be explained by a polygenic architecture influenced by variable penetrance and co-segregation rather than a classic Mendelian inheritance pattern of a single genetic variant.[6]

CM & Co-Morbidities:

- The possibility of genetic transmission of CM is further enhanced by its association with known genetic disorders, suggesting potential co-segregation.[6]
- CM1 with connective tissue disorders (i.e., Ehlers Danlos Syndrome) may have a different pathological mechanism, thus, is driven by different genes than CM1 without connective tissue disorders.[7]

Future Research Directions:

1. To increase genomic approaches (i.e., epigenetic analyses, next generation sequencing) to repeatedly identify candidate gene(s) with larger sample sizes and a variety of ethnicities.[8]
2. To create genetically homogenous subsets by stratifying CM based on co-occurring genetic disorders to improve power of localizing susceptibility genes when performing linkage analyses.[9]

CONCLUSIONS

1. **Suspect:** All first-degree relatives even if asymptomatic should undergo close monitoring, comprehensive neurological exams, and routine brain and complete spine MRIs if possible to facilitate early diagnosis of CM**.**
2. **Educate:** CM symptoms can be vague, heterogenous, slowly progressive, misdiagnosed, or mased by certain medications.
3. **Test:** Genetic testing using next generation sequencing technology can further establish a genetic linkage & the prevalence of other comorbidities should lower the threshold for further CM workup.

REFERENCES

1. Crimmins DW, Palmer JD. Arnold Chiari, or "Cruveilhier Cleland Chiari" malformation. *J Neurol Neurosurg Psychiatry*. 2000;68(1):13-13. doi:10.1136/JNNP.68.1.13
2. Kular S, Cascella M. Chiari I Malformation. *StatPearls*. Published online February 5, 2022. https://www.ncbi.nlm.nih.gov/books/NBK554609/
3. Shanker BD, Walcott BP, Nahed B V., Kahle KT, Li YM, Coumans JVCE. Familial Chiari malformation: case series. *Neurosurg Focus*. 2011;31(3). doi:10.3171/2011.6.FOCUS11104
4. Rocky Mountain Brain & Spine Institute. Chiari Malformation. *Rocky Mountain Brain & Spine Institute*. *https://rockymountainbrainandspineinstitute.com/chiari-malformation/*
5. Mba C, Milhorat TH. Chiari I Malformation Redefined: Clinical and Radiographic Findings for 364 Symptomatic Patients [Clinical Studies]. *Congress of Neurological Surgeons*. 1999;44(5):1005-1017. http://gateway2.ovid.com/ovidweb.cgi
6. Capra V, Iacomino M, Accogli A, et al. Chiari malformation type I: what information from the genetics? doi:10.1007/s00381-019-04322-w
7. Urbizu AI, Garrett ID ME, Soldano KI, et al. Rare functional genetic variants in COL7A1, COL6A5, COL1A2 and COL5A2 frequently occur in Chiari Malformation Type 1. Published online 2021. doi:10.1371/journal.pone.0251289
8. Urbizu A, Khan TN, Ae AK. Genetic dissection of Chiari malformation type 1 using endophenotypes and stratification. *J Rare Dis Res Treat*. 2017;2(2):35-42. www.rarediseasesjournal.com
9. Markunas CA, Soldano K, Dunlap K, et al. Stratified whole genome linkage analysis of Chiari type I malformation implicates known Klippel-Feil syndrome genes as putative disease candidates. *PLoS One*. 2013;8(4):e61521. Published 2013 Apr 19. doi:10.1371/journal.pone.0061521