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Original Article

Prevalence and Impact of Underlying Diagnosis and Comorbidities on Chiari 1 Malformation

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ABSTRACT

Background: Chiari malformation type 1 affects approximately one in 1,000 people symptomatically, although one in 100 meet radiological criteria, making it a common neurological disorder. The diagnosis of underlying conditions has become more sophisticated, and new radiological markers of disease have been described. We sought to determine the prevalence and impact of additional comorbidities and underlying diagnoses in patients with Chiari malformation type 1 on symptomatology and surgical treatment.

Methods: A retrospective review of 612 pediatric patients with a Chiari malformation type 1 diagnosis and imaging data evaluated between 2008 and 2018 was performed. Because of extensive clinical heterogeneity, patients were separated into four categories based on their primary comorbidities (nonsyndromic, central nervous system, skeletal, and multiple congenital anomalies) to identify associations with age of onset, radiographic measurements, syringomyelia, and surgical treatment.

Results: The largest group had nonsyndromic Chiari malformation type 1 (70%) and the latest age at diagnosis of any group. In the syndromic group, 6% were diagnosed with a known genetic abnormality, with overgrowth syndromes being the most common. Patients with multiple congenital anomalies had the earliest Chiari malformation type 1 onset, the most severe tonsillar ectopia and obex position, and were overrepresented among surgical cases. Although there were no statistically significant differences between groups and rates of syrinx, we observed differences in individual diagnoses.

Conclusion: The underlying diagnoses and presence of comorbidities in patients with Chiari malformation type 1 impacts rates of syringomyelia and surgery. Although most Chiari malformation type 1 cases are nonsyndromic, clinical evaluation of growth parameters, scoliosis, and joint hypermobility should be routine for all patients as they are useful to determine syringomyelia risk and may impact treatment.

Introduction

Chiari malformation type 1 (CM1) affects one in 1000 individuals symptomatically and may be observed radiologically in up to 1% to 3.6% of magnetic resonance imaging (MRI),[1-3] making it a common disorder that represents a substantial personal, familial, and societal burden. Patients present with a wide array of symptoms from the CM1 itself or from craniovertebral instability,

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syringomyelia, hydrocephalus, or other causes.[4] In fact, approximately 25% patients with CM1 develop syringomyelia, a fluid-filled cyst in the spinal cord that can result in motor and sensory deficits and urinary incontinence. Syringomyelia occurs in as many as 75% surgical CM1 cases as decompressive surgery is often indicated to reduce ongoing spinal cord compression.[3] About 20% patients with CM1 develop scoliosis, although this figure increases to 60% when syringomyelia is present.[5]

Understanding the disorders associated with CM1 is essential to improve surgical and nonsurgical treatment strategies that will translate into improved quality of life for patients. CM1 is typically considered a congenital defect, but it can also rarely be acquired due to trauma.[6] Clinical heterogeneity is a major challenge,[7] as CM1 often occurs in the context of a myriad of diseases and disorders[8] where it may be noted incidentally or represent a significant pathologic focus. The exact frequency of comorbidities or underlying diagnoses in CM1 has not been well established, and CM1 outcomes are not well documented in patients with rare known genetic disease. One study, using MRI examinations to identify abnormalities, reported that approximately 25% patients with CM1 had a syrinx and ~35% had incidental radiographic findings such as Klippel-Feil syndrome or platybasia.[3] In 2011, Loukas et al.[8] reported more than 50 disorders associated with CM1, suggesting significant genetic heterogeneity. However, over time, both genetic studies and imaging methods have increased in quality and become more common, therefore the current data may allow us to provide a better estimate of the number of cases that are nonsyndromic.

Here, we report the incidence of nonsyndromic CM1 versus CM1 with additional comorbidities or known genetic syndromes, as well as radiographic measures within each subgroup in a large clinical cohort of neurosurgery patients treated at a tertiary academic medical center. We document the extensive heterogeneity of associated conditions that were identified during routine clinical care in the syndromic cases, as we consider it likely that similar underlying biologic mechanisms may be involved in the nonsyndromic cases. We also sought to determine whether the presence of an associated disorder impacts clinical features, including age of onset, radiographic measures of severity, presence of syringomyelia, and surgical treatment with posterior fossa decompression (PFD). By categorizing CM1 cases based on comorbid symptoms and examining the disease severity in each comorbidity group, we can help elucidate the underlying mechanisms of this disease, which can help guide treatment.

Methods

After Institutional Review Board approval from Washington University in St. Louis, retrospective chart review of all patients with CM1 seen in St. Louis Children's Hospital from 2008 to 2018 was performed by screening all pediatric neurosurgery clinics for patients with a CM1 diagnosis (N = 612). Diagnosis was made using radiographic criteria of cerebellar tonsil ectopia of at least 5 mm.[9] Obex position was measured on radiographs as the distance of the obex from the foramen magnum as defined by the basion-opisthion line.[10,11] Magnetic reaonance images were evaluated to determine posterior cranial fossa measurements according to Tubbs et al.[10] using midline sagittal T1-weighted image. Additional clinical data collected include sex, ethnicity, presenting signs and symptoms, presence and degree of scoliosis, presence of syringomyelia, and treatment course. Family history was documented, and additional medical problems were recorded. Imaging controls (N = 50) were identified among patients seen for headaches at pediatric neurology clinics at St. Louis Children's Hospital who were not found to have tonsillar herniation or other intracranial pathology.

To account for extensive etiologic heterogeneity, patients were grouped into four categories based on their comorbid conditions, including central nervous system (CNS), skeletal, multiple congenital anomalies, and nonsyndromic (Fig 1). The nonsyndromic group was defined by not having major comorbidities or underlying diagnoses, although scoliosis and common neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder, anxiety, depression, obsessive-compulsive disorder, and oppositional defiant disorder were allowed, as was the presence of syringomyelia, where noted by the treating physician or radiologist. Information on additional comorbidities was considered when grouping the patients. For example, designation of multiple congenital anomalies required more than one comorbidity, such as CNS, skeletal, cardiac, or other major organ system involvement. Patients in the multiple congenital abnormalities (MCA) group were the only ones whose additional comorbidities may have been directly related to the Chiari (i.e., tethered cord and spina bifida occulta). Patients in the other groups had either no secondary comorbidities or no unrelated comorbidities, such as mental health, dermatologic conditions, allergies, etc. To determine what proportion of each group presented incidentally or as part of routine evaluation for their disease, we reviewed each patient's indication for MRI. The indications for surgery in those having undergone PFD were documented by the treating neurosurgeon after chart review.

Correlations were made between category and clinical features, including age of onset, presence of syringomyelia, tonsillar ectopia, and obex position. Because the data were normally distributed, two-tailed t tests were performed to determine significance.

Results

Overall, the average age of the 612 patients in this cohort was 15 years with 52% female and 48% male. After reviewing the clinical data, including imaging and genetic test results acquired during routine care, we found that the vast majority of patients (70%) had nonsyndromic CM1 (Fig 1). The nonsyndromic group was defined by not having major comorbidities or underlying diagnoses, although idiopathic scoliosis and common neuropsychiatric

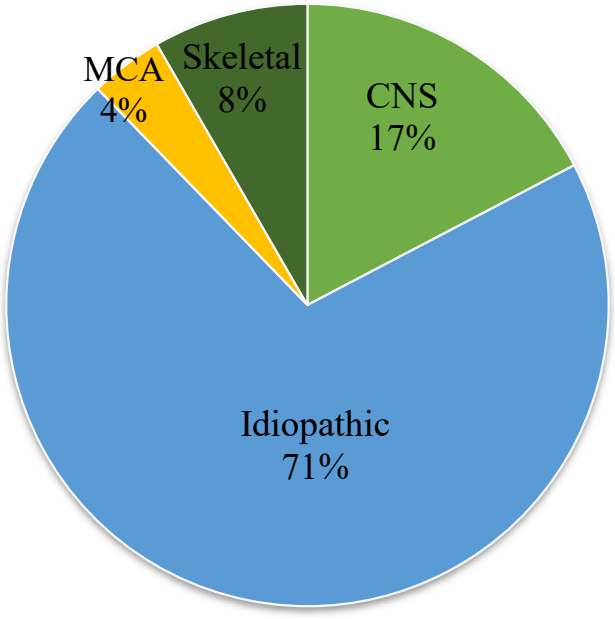

FIGURE 1. Distribution of comorbidities of patients in the samples. The color version of this figure is available in the online edition.

TABLE 1.
Prevalence of Genetic Disorders in 612 Patients in the CM1 Cohort

Genetic Disorders	No. of Cases (%)
Overgrowth syndromes	15 (2.1)
Neurofibromatosis type I (3), neurofibromatosis type II (2), Sturge-Weber (2), McCune-Albright, Beckwith-Wiedemann, cutis marmorata telangiectatica congenita, Klippel-Trenaunay, *PIK3R2*, CLOVES, Tatton-Brown-Rahman, Noonan syndrome, Osler-Weber-Rendu, tuberous sclerosis	
Genomic copy number variants	10 (1.6)
2p21p16.2 deletion (2), 13p partial trisomy, Pierre Robin sequence, 4q31 deletion, Xp22.33 duplication, 15q33.3 triplicate, 3p25.3 deletion, Trisomy 21, 15q13.2q13.3 deletion	
Ehlers-Danlos syndrome type 3	7 (1.1)
Loeys-Dietz syndrome	2 (0.3)
Achondroplasia	1 (0.2)
Alagille syndrome	1 (0.2)
Congenital adrenal hyperplasia	1 (0.2)
Crouzon syndrome	1 (0.2)
Duane syndrome	1 (0.2)
Muenke syndrome	1 (0.2)
Sickle cell disease	1 (0.2)

disorders, such as attention-deficit/hyperactivity disorder, anxiety, depression, obsessive-compulsive disorder, and oppositional defiant disorder were allowed.

Genetic diagnoses in the sample

When chromosomal abnormalities were included, 6% of our patients were diagnosed with a genetic abnormality as part of their routine clinical evaluations (Table 1). A total of 25 specific genetic conditions or syndromes were observed in at least one patient with CM1 in our cohort. The largest number of patients had an overgrowth syndrome, which is commonly defined by macrocephaly and either somatic or germline mutations in one of the genes involved in growth.[12] These patients include those diagnosed with neurofibromatosis types 1 and 2, tuberous sclerosis complex, Klippel-Trenaunay syndrome, Sturge-Weber syndrome, and several other rare disorders, several of which require sequencing of affected tissues for diagnosis. In addition, Ehlers-Danlos syndrome type 3 (hypermobility type) was the single most common clinical "genetic" diagnosis, although it cannot be tested for genetically as the causative gene or genes have not yet been identified. None of these individual genetic disorders had statistically significantly higher rates of syringomyelia or surgery compared with other comorbidities or underlying diagnoses, possibly due to low sample size. When all patients with underlying genetic conditions or syndromes were combined, 30% had a syrinx and 30% had PFDs.

Comparison between the groups of patients with CM1

We also sought to determine whether the etiology or the presence of comorbidities resulted in differences in age of onset, radiographic measurements of severity, syringomyelia, or surgical treatment with PFD. To account for extensive heterogeneity and small individual sample size, patients were grouped into four categories based on their comorbid conditions, including CNS, skeletal, multiple congenital anomalies, and nonsyndromic (Fig 1). Designation of multiple congenital anomalies required more than one comorbidity, such as CNS, skeletal, cardiac, or other major organ system involvement (Table S1). Patients with CNS abnormalities had comorbidities such as hydrocephalus, tethered cord, growth hormone/pituitary abnormalities, cerebral abnormalities such as arachnoid cysts, autism/developmental delay, and epilepsy. Skeletal comorbidities include hypermobility/joint laxity, craniosynostosis, platybasia, and congenital scoliosis (Table 2). Patients with a known genetic disorder were placed in the category characterized based on their primary comorbid diagnosis.

Age at CM1 diagnosis

Average age at diagnosis was significantly higher for patients with nonsyndromic CM1 compared with the other three groups. The age at CM1 diagnosis when macrocephaly, hydrocephalus, or ventriculomegaly was present was approximately two years, which was the youngest among individual conditions. When groups of conditions were considered, the age at diagnosis was the lowest for the MCA group (5.6 years) and the highest for the nonsyndromic group (10.3 years) (Fig 3). This difference was statistically significant between the nonsyndromic group and all three other groups ($10^{-5}<P<10^{-4}$).

Tonsillar ectopia and obex position

To determine if radiographic markers of severity differ among groups, we compared average tonsillar ectopia. Tonsillar descent was greatest in the MCA group (12.3 mm) and lowest in the CNS group (9.3 mm), and the difference between the two was statistically significant ($P = 0.002$). More recently, a recurring complex Chiari malformation presentation led to the description of the Chiari 1.5 malformation, which is associated with obex (brainstem) ectopia below the McRae line (also known as basion-opisthion line) and a more severe presentation that often requires PFD surgery.[10,11] Obex measurement is shown in Fig 2.[10,11] To interpret the obex measurement, a smaller number indicates greater caudal descent, with those below the McRae line being the worst and having negative values. The average obex in the entire present cohort was +2.3 mm. In non-Chiari controls (N = 50), the average tonsillar position was 9 mm above the foramen magnum and the average obex was +10 mm (manuscript submitted). The skeletal group had a smaller mean obex measurement than all other groups, including the largest proportion with negative measurements of all groups (37%), although the difference was only significant between the skeletal and MCA groups, with the MCA group having a higher average obex position (Table 2). In fact, the MCA group had a higher obex than the sample average.

Syringomyelia

Because the occurrence of syringomyelia may lead to neurological deficits and is often an indication for surgery,[13] we sought to determine if there were differences in its prevalence between diagnostic groups. More than 95% patients with syringomyelia had a spinal MRI available for review.

Syringomyelia was present in 40% patients with joint hypermobility, as well as in 40% patients with ventriculomegaly and 29% patients with hydrocephalus. When data were considered within groups, the skeletal group had a 30% rate of syringomyelia (Table 2) and all others had rates of approximately 25%, although this difference was not statistically significant. Patients within the MCA and skeletal comorbidity groups were diagnosed slightly earlier when a syrinx was present (Fig 3), although this was also not statistically significant.

Posterior fossa decompression surgery

We then determined whether the presence of additional comorbidities and underlying diagnoses impacted the proportion of patients receiving posterior decompression surgery for Chiari symptoms (Table 2). Patients with platybasia, tethered cord or other spinal anomalies, growth hormone deficiency, and craniosynostosis all had surgery rates greater than 50%. The skeletal and MCA groups had higher rates of PFD surgery (47% and 42%,

TABLE 2.
Primary Comorbidities and Clinical Features of Patients With CM1

Comorbidity	N, % of Sample	Avg. Age at CM1 Diagnosis (yr)	Avg. Tonsillar Ectopia (mm)	Avg. Obex Descent (mm)	% With Syrinx	% Receiving PFD
Central nervous system	113 (18%)	7.9	9.3	+2.58	26	30
Epilepsy	19	6.2	10.1	+2.92	22	17.6
Hydrocephalus	17	2.3	10.4	−0.09	29	35.3
Autism/developmental delay	14	9	10.1	+3.11	0	20
Growth hormone/pituitary	13	7.7	10.1	+3.42	18	54.5
Arachnoid/cerebral cysts	12	10.5	8.0	+3.31	18	9.1
Ventriculomegaly	7	2	7.0	+5.95	40	14.2
Tethered cord/spinal anomaly	7	5	7.7	+3.90	43	57
Pseudotumor cerebri	5	16	9.1	−0.45	20	20
Macrocephaly	5	1.2	10.2	+3.10	20	25
Cerebral palsy	4	5	7.5	−2.40	0	75
Cortical malformations	4	7	5.0	+0.65	0	0
White matter abnormality	4	9.5	11.5	+1.05	0	50
Stroke/intraventricular hemorrhage	2	1.5	8.5	+9.65	0	50
Skeletal	47 (8%)	6.8	10.1	+1.06	30	47
Hypermobility/joint laxity	15	8.6	9.3	+3.48	40	26.6
Craniosynostosis	8	5	8.5	+3.56	25	50
Platybasia	7	8.4	15.3	−0.76	14	57.1
Other bone malformations	5	3	8.8	−3.60	20	40
Congenital scoliosis	3	15.3	7.3	−2.23	0	67
Congenital torticollis	2	11	22.5	Unknown	0	0
Pyriform aperture stenosis	2	5	9.0	−3.65	0	50
Hemivertebrae	2	3	11.0	−4.45	50	50
Vitamin D rickets	1	13	13.0	+1.4	0	0
Spinal trauma	1	8	17.0	Unknown	0	0
Multiple congenital anomalies	26 (4%)	5.6	12.3	+5.02	27	42
Idiopathic	427 (70%)	10.3	10.0	+2.19	26	37
Overall sample	612 (100%)	9.4	10.0	+2.30	25	38

respectively) than the overall sample average (38%), although the difference was only statistically significant between the skeletal and CNS subgroups ($P = 0.05$). The two groups with the highest rates of surgery were those with the most severe average tonsillar ectopia (MCA) and obex measurement (skeletal). We then reviewed the indications for PFD surgery and found that in those undergoing PFD surgery, 40% had surgery due to syringomyelia, 40% due to headaches, 5% due to scoliosis, 2% each due to dysphagia and sleep apnea, and neck pain, weakness, and vision changes making up the remainder.

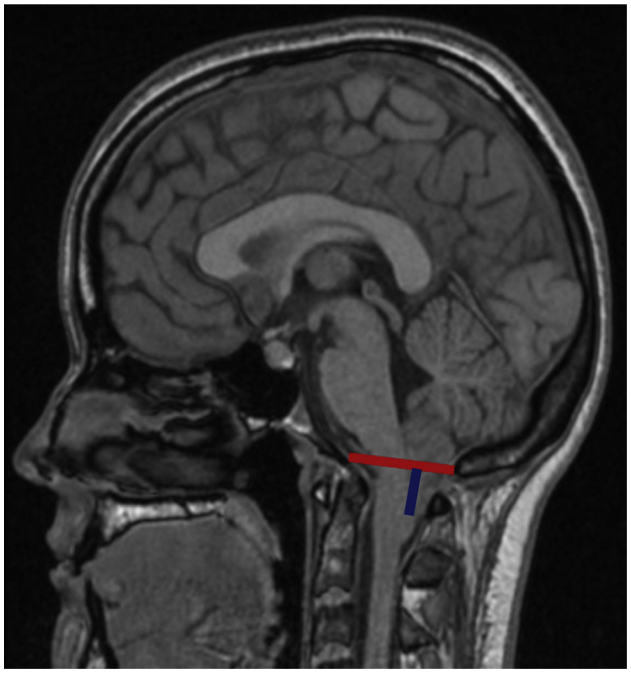

FIGURE 2. Midline sagittal T1-weighted magnetic resonance image of a patient with CM1 showing McRae line also known as basion-opisthion line (red) and obex position (blue).[10,11] The color version of this figure is available in the online edition.

Incidental Chiari 1 malformation

Approximately 50% patients in our cohort had their CM1 discovered incidentally based on original MRI review. Not surprisingly, over half of these were in nonsyndromic cases. As CM1 is a neurological disorder, some of these symptoms for which the MRI was ordered may have been related to the Chiari after all and not, in fact, incidental. When removing patients whose MRIs were for symptoms that may be related to CM1, for example, scoliosis, syringomyelia, hydrocephalus, tethered cord, craniosynostosis, epilepsy, etc., the number of incidental CM1 cases dropped to 27%. Of these incidental cases without any CM1-related symptoms or disorders, 65% were nonsyndromic, 20% were CNS, 7% skeletal, and 6% MCA. These numbers are nearly identical to the breakdown of patients in the entire sample (Fig 1).

Discussion

Within our tertiary referral center the vast majority of patients have nonsyndromic CM1 (70%) despite the widespread use of sophisticated imaging methods and genetic testing. About 6% patients had a specific genetic diagnosis, which is higher than earlier estimates of 1%.[1] When they are present, underlying diagnoses and additional comorbidities are very heterogeneous, suggesting that there are many potential pathways that lead to the cerebellar tonsil ectopia that characterizes CM1.

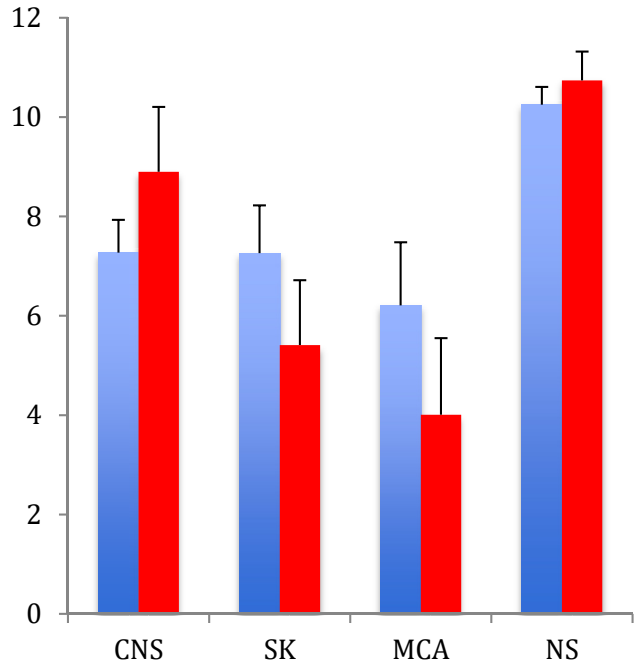

FIGURE 3. Age at diagnosis is associated with comorbidities and presence of syringomyelia. Age at diagnosis of CM1 with (red) and without (blue) a syrinx. Patients with CM1 and multiple congenital anomalies are diagnosed earlier, particularly when a syrinx is present. CNS, central nervous system; SK, skeletal; MCA, multiple congenital anomalies; NS, nonsyndromic. The color version of this figure is available in the online edition.

Connective tissue disease and overgrowth syndromes overrepresented in CM1 cases

Ehlers-Danlos syndrome type 3 (hypermobility type) or self-reported hypermobility was commonly noted in our study, which is consistent with a prior identification of connective tissue disorder in ~10% patients with CM1.[14] Unlike the study just referenced, the patients in our retrospective study were not routinely asked about or systematically tested for joint hypermobility; therefore our numbers underestimate its prevalence. Notably, clinical evaluation for joint hypermobility can be performed simply and without special equipment using the Beighton quantitative scoring system,[15] which should become a standard part of the clinical evaluation of CM1, not only because of the frequency of this comorbidity but also because cardiac and systemic abnormalities often associated with connective tissue disorders can be better managed if the diagnosis is made early. We also identified a large number of patients with overgrowth syndromes, which have recently been shown in some cases to be due to low-level somatic mosaicism[16,17] and may not have been diagnosed before the common use of genetic testing. Overgrowth as an etiologic cause for CM1 is also supported by the co-occurrence of CM1 in neurofibromatosis type 1, Noonan syndrome, and tuberous sclerosis complex, which are closely related to the somatic disorders due to their growth abnormalities, although they are associated with germline genetic variants.

Importance of understanding clinical heterogeneity in CM1

Our outcome data suggest that it is important to understand the underlying etiologies and comorbidities with CM1, as patients may have differing rates of syringomyelia and surgery. For example, compared with the entire CM1 cohort, which had a 25% risk of syringomyelia, we found that patients with joint hypermobility had a slightly higher rate (40%), whereas syringomyelia was not present in any of our patients with unspecified autism/developmental delay. Because the underlying causes of autism/developmental delay are so heterogeneous, further study is clearly needed to better predict outcomes. Syringomyelia was slightly higher in patients within the skeletal group of comorbidities. Although we excluded patients with adolescent idiopathic scoliosis from the skeletal group due to its nonsyndromic nature, it is well known that patients with CM1 and scoliosis have high rates of syringomyelia[18-20] and 8% of presumed pediatric idiopathic scoliosis cases were found upon MRI to have CM1.[21] Among other studies examining comorbid conditions, it was recently determined that among patients with CM1, hydrocephalus and syringomyelia were the most common concurrent diagnoses, followed by scoliosis and tethered cord.[22]

Patients with multiple congenital anomalies in our sample, not surprisingly, had the earliest diagnosis and the highest rates of PFD surgery, likely reflecting both the severity of disease and earlier imaging that often occurs in children with complex medical conditions. It is likely that earlier symptoms as well as increased number of symptoms in these children drive earlier imaging. Indeed, children with complex chronic conditions that include hydrocephalus have a significantly higher risk of surgical complications,[19] and this association was especially significant in younger children.[23] Nonsyndromic CM1 may represent a milder form of the disease, which is supported by the latest age at diagnosis of any of the groups, and its underrepresentation among surgical cases. Because our study cohort was recruited primarily from neurosurgery clinic, the rates of surgery in nonsyndromic cases may have been even lower if more asymptomatic, nonreferred patients were included.

PFD surgery is costly and invasive, and depending on the cause of the CM1, not always successful.[14] Thus, determining which patients are more likely to need surgery is important. We determined that patients with platybasia and patients with growth hormone or pituitary abnormalities, which have both been previously associated with high rates of CM1,[8,24] are more likely to have surgery. The MCA and skeletal comorbidity groups had the most severe tonsillar ectopia and obex (12.13 and 1.29 mm, respectively) and are also overrepresented among surgical cases, suggesting that they have some of the more severe CM1 presentations.

Limitations

A limitation of this study is that, due to its retrospective nature, not all patients received the same testing, whether that was clinical evaluations for joint hypermobility, diagnostic testing for endocrine abnormalities, or genetic testing or spinal cord imaging. Therefore, we may have underestimated the frequency of associated comorbidities. The data in this study also represent a single point in time; therefore some of these patients may have developed syringomyelia or required surgery later in their care, or this may have been performed elsewhere. In addition, we do not have data on syrinx size for all patients and so could not perform association testing on the size of the syrinx itself. We also note that CM1 occurs frequently in patients with craniosynostosis, but these cases are underrepresented here because most are typically asymptomatic and, at our center, managed entirely by the craniofacial team. In addition, there may be a referral bias toward symptomatic patients as these patients were ascertained at a pediatric neurosurgical referral center. Last, we note that classification systems of any kind will have their unique issues. We grouped our patients into these four subtypes not only for increased power in analysis but also as an attempt to address and understand their complex clinical presentations.

Implications for patients

Overall, our data suggest that there are multiple etiologic pathways that converge on the Chiari 1 malformation phenotype. Although most patients have nonsyndromic CM1 and no underlying genetic abnormality or associated comorbidity, this study suggests that a thorough clinical assessment of patients with CM1 should include evaluation of head circumference and height to evaluate for possible endocrine abnormality or connective tissue disorder, clinical scoliosis examination (Adam's forward bend test), and Beighton test for joint hypermobility. These simple clinical examination findings would aid the diagnosis and recognition of some of the most commonly associated CM1 conditions. Our data suggest that it is important to consider evaluation of underlying etiologies, such as overgrowth syndromes or hypermobility syndromes, among others, as these patients have differing rates of syringomyelia and surgery.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2019.12.005.

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