Chiari I Malformation Redefined: Clinical and Radiographic Findings for 364 Symptomatic Patients

[Clinical Studies]

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Outline

Graphics

Abstract ⊞

OBJECTIVE: Chiari malformations are regarded as a pathological continuum of hindbrain maldevelopments characterized by downward herniation of the cerebellar tonsils. The Chiari I malformation (CMI) is defined as tonsillar herniation of at least 3 to 5 mm below the foramen magnum. Increased detection of CMI has emphasized the need for more information regarding the clinical features of the disorder.

METHODS: We examined a prospective cohort of 364 symptomatic patients. All patients underwent magnetic resonance imaging of the head and spine, and some were evaluated using CINE-magnetic resonance imaging and other neurodiagnostic tests. For 50 patients and 50 age- and gender-matched control subjects, the volume of the posterior cranial fossa was calculated by the Cavalieri method. The families of 21 patients participated in a study of familial aggregation.

RESULTS: There were 275 female and 89 male patients. The age of onset was 24.9 +/- 15.8 years (mean +/- standard deviation), and 89 patients (24%) cited trauma as the precipitating event. Common associated problems included syringomyelia (65%), scoliosis (42%), and basilar invagination (12%). Forty-three patients (12%) reported positive family histories of CMI or syringomyelia. Pedigrees for 21 families showed patterns consistent with autosomal dominant or recessive inheritance. The clinical syndrome of CMI was found to consist of the following: 1) headaches, 2) pseudotumor-like episodes, 3) a Meniere's disease-like syndrome, 4) lower cranial nerve signs, and 5) spinal cord disturbances in the absence of syringomyelia. The most consistent magnetic resonance imaging findings were obliteration of the retrocerebellar cerebrospinal fluid spaces (364 patients), tonsillar herniation of at least 5 mm (332 patients), and varying degrees of cranial base dysplasia. Volumetric calculations for the posterior cranial fossa revealed a significant reduction of total volume (mean, 13.4 ml) and a 40% reduction of cerebrospinal fluid volume (mean, 10.8 ml), with normal brain volume.

CONCLUSION: These data support accumulating evidence that CMI is a disorder of the para-axial mesoderm that is characterized by underdevelopment of the posterior cranial fossa and overcrowding of the normally developed hindbrain. Tonsillar herniation of less than 5 mm does not exclude the diagnosis. Clinical manifestations of CMI seem to be related to cerebrospinal fluid disturbances (which are responsible for headaches, pseudotumor-like episodes, endolymphatic hydrops, syringomyelia, and hydrocephalus) and direct compression of nervous tissue. The demonstration of familial aggregation suggests a genetic component of transmission.

The Chiari I malformation (CMI) is a disorder of uncertain origin that has been traditionally defined as downward herniation of the cerebellar tonsils through the foramen magnum (12,26,32,35,71,78). The anomaly is a leading cause of syringomyelia (12,32,61,65,78) and occurs in association with osseus abnormalities at the craniovertebral junction. In contrast to other Chiari malformations, CMI tends to present in the second or third decade of life and is sometimes referred to as the "adult-type" Chiari malformation. CMI is distinguished from the more familiar Chiari II malformation, which is present at birth and consists of downward herniation of the lower cerebellum and medulla into the spinal canal, in association with myelodysplasia and complex anomalies of the brain such as aqueductal forking and polymicrogyria (14,60). The comparatively rare Chiari III malformation is also present at birth and is defined as cerebellar herniation into a cervical encephalocele (26,60). From a developmental standpoint, Chiari malformations have been classified as neuroectodermal defects (14,59), although there is accumulating evidence that tonsillar herniation in CMI is attributable to overcrowding of the hindbrain by an underdeveloped posterior cranial fossa (PCF) (10,35,54,55,71,72,86,96,102).

Current interest in CMI can be attributed to magnetic resonance imaging (MRI), which has revolutionized diagnosis and has led to the detection of cases that either were not recognized or were erroneously identified as other conditions. The resulting increase in the number of reported cases has emphasized the need for greater understanding of the pathogenesis and clinical manifestations of CMI. Growing concerns regarding the risk of inheritance cannot be answered on the basis of case reports of familial aggregation (9,23,39,92).

To investigate the syndrome of CMI, we studied a prospective cohort of 364 symptomatic patients, including those with ambiguous or unfamiliar symptoms. The study provides a comprehensive review of the symptoms, neurodiagnostic findings, and inheritance patterns for this group of patients.

PATIENTS AND METHODS
Patients

Three hundred sixty-four patients who had been referred for evaluation of CMI were studied prospectively between January 1994 and December 1997 (Table 1). To be eligible for the study, each patient was required to be symptomatic and to have MRI findings consistent with CMI or an anomaly of the basichondrocranium in association with syringomyelia. A total of 107 patients (29%) had undergone surgical treatment for CMI or syringomyelia. The requirements for enrollment of the latter patients included access to all preoperative medical records, radiographic studies, and neurological findings. Patients with neurological deficits attributable to surgery were excluded.

Variable	CMI (n = 126)	CMI/SM (n = 238)	All Patients (n = 364)
Gender (M/F)	32/94	57/181	89/275
Age (yr)[b]	33.7 ± 15.2	37.1 ± 17.7	35.9 ± 16.8
Prior surgical treatment (no. of patients)	12	95	107
Clinical presentation			
Lifelong complaints (no. of patients)[c]	50	84	134
Age of onset (yr)[b, d]	25.2 ± 14.2	24.7 ± 16.6	24.9 ± 15.8
Definitive diagnosis (yr)[b]	31.7 ± 14.7	30.3 ± 16.2	30.8 ± 15.7
Precipitating factors (no. of patients)			
None	74	119	193
Trauma[e]	23	66	89
Infection	11	16	27
Coughing or sneezing	9	15	24
Pregnancy	3	13	16
Other[f]	6	9	15

[a] CMI, Chiari I malformation; SM, syringomyelia.
[b] Values are means ± standard deviations.
[c] Not included in determining the age of onset.
[d] Defined as the time when the patient first sought medical attention.
[e] Includes whiplash injuries and direct blows to the head or neck.
[f] Includes sexual intercourse, epidural anesthesia, lumbar puncture, and air travel.

TABLE 1. Characteristics of the Patients and Clinical Presentation[a]

Baseline assessments

A database (Microsoft Access) was established for each patient and included the history of pregnancy and delivery, maternal exposure to toxic substances, potential environmental exposure, medical history, family history, a detailed checklist of symptoms, and a questionnaire developed by the American Syringomyelia Alliance Project to elicit information regarding the familial incidence of CMI. All patients underwent a physical examination, a complete neurological examination, and MRI of the head and spine. In some cases, additional information was provided by computed tomography, CINE-MRI, vestibular function tests, audiometry, continuous cardiac monitoring, 24-hour sleep monitoring, and other diagnostic tests. The clinical disability of each patient was measured using a Karnofsky performance scale of 0 to 100 (45). Karnofsky scores for patients who had undergone previous surgical treatment were based on preoperative clinical disability.

Morphological features of the PCF

The morphological features of the PCF were investigated using MRI. For 50 randomly selected adult patients and 50 age- and gender-matched control subjects who had undergone MRI for nonspecific complaints and showed no evidence of cranial or intracranial disease, the following measurements were made in midline sagittal images: 1) the length of the supraocciput was measured from the center of the internal occipital protuberance to the opisthion, 2) the length of the clivus (basiocciput and basisphenoid) was measured from the top of the dorsum sella to the basion, 3) the slope of the tentorium was calculated by measuring the angle formed by the tentorium and a line drawn between the internal occipital protuberance and the opisthion, and 4) the extent of cerebellar herniation was measured from the tips of the cerebellar tonsils to a line drawn between the basion and the opisthion (Fig. 1).
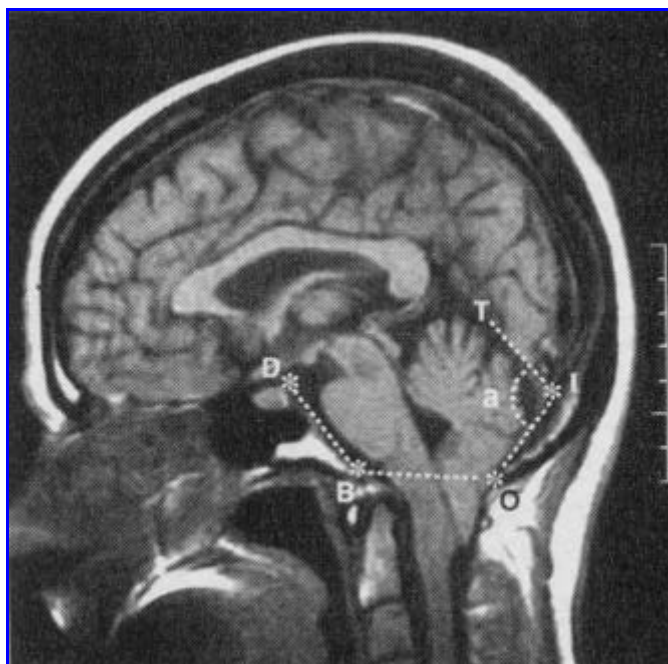
FIGURE 1. Measurements of PCF morphological characteristics using T1-weighted sagittal MRI scans of a 44-year-old female patient with CMI. The length of the supraocciput (*IO*) was measured along a line drawn from the center of the internal occipital protuberance (*I*) to the opisthion (*O*). The length of the clivus (*DB*) was measured along a line drawn from the top of the dorsum sella (*D*) to the basion (*B*). The slope of the tentorium (*T*) was calculated by measuring the angle (*a*) formed by the tentorium and the supraocciput. The extent of tonsillar herniation was measured from the tips of the cerebellar tonsils to a line drawn between the basion and the opisthion. Findings in this case consisted of a short supraocciput, increased slope of the tentorium, hypoplasia of the clivus, and descent of the cerebellar tonsils 1.6 cm below the foramen magnum.

For all other patients, brain and osseus structures were assessed qualitatively. The slope of the tentorium and the length of osseus structures were defined subjectively as normal, increased, or decreased, based on measurement parameters for 50 control subjects. We defined odontoid retroflexion as inclination of the tip of the odontoid process more than 15 degrees posterior to a line drawn from the midbody of C2 to the basion in midline sagittal images. For 47 patients who underwent phase-contrast CINE-MRI, decreased cerebrospinal fluid (CSF) velocity/flow was defined as the absence of observed CSF in the subarachnoid spaces posterior or anterior to the cervicomedullary junction.

Volume of the PCF

The PCF was defined as the almost circular space bounded by the tentorium, occipital bone, clivus, and petrous ridges. Volumetric calculations were made using the Cavalieri method (28,40,58,74,82), which is simpler and quicker than computer-based programs (28) and provides results that are closely correlated with those achieved using other methods (40,82). All calculations were made by a single experienced observer who was unaware of other study data, to avoid interobserver variability, which can increase the coefficient of error to more than 5% (28). The results were reviewed independently by two experienced observers, who oversaw the process and verified all calculations.

Three variables were calculated, i.e., total PCF volume, CSF volume of the PCF, and brain volume of the PCF. Using axial MRI images, a series of equally spaced slices of the PCF having a combined thickness and interslice gap of 4 to 7 mm (mean +/- standard deviation, 5.2 +/- 0.9 mm) were selected from images on the hard copy of each scan, using the table positions reported

on the scan. A clear plastic sheet with an imprinted grid of 4-mm, regularly spaced points was placed over 7 to 12 (mean +/- standard deviation, 8.5 +/- 1.2) consecutive axial images, and the number of points falling within the PCF on each slice (Pi) was counted. The minimal number of points for each scan was 117 (mean +/- standard deviation, 141 +/- 10.5), which produces a coefficient of error of less than 5% (28). The true anatomic distance between two consecutive points on the grid was established by counting the number of points along a line placed over the centimeter ruler of the scan, thereby correlating the grid with the field of view of the scan. When necessary, the centimeter ruler was extended to establish an integer number of points and a whole number of centimeters. To calculate the area associated with each point (Ap), the anatomic distance between two consecutive points was squared. The sum of the points that fell within the PCF ([SIGMA]Pi) was multiplied by Ap and the distance between slices (T) to calculate volume (V), using the following equation: $V = T$ [middle dot] Ap [middle dot] [SIGMA]Pi. Calculations of CSF and brain volumes were made separately on each scan. Measurements of the PCF, including the extent of tonsillar herniation, were compared with previously published data (1,10,13,71,72,94,96,102).

Pedigree development and assessment of familial aggregation ⊡

Twenty-one families participated in a study of familial aggregation. The protocol for the study was reviewed and approved by the Institutional Review Board of Duke University Medical Center. Written informed consent was received from each family. Photographs of all prospective probands were reviewed by a dysmorphologist to exclude individuals with a known genetic syndrome. The medical records and MRI scans of prospective affected relatives were examined to confirm the diagnosis of CMI. The database was expanded to include each affected family member. After the inclusion criteria of the study had been met, a pedigree was established for each family.

Statistical analyses ⊡

The statistical analyses were performed with SPSS for Windows (version 7.5; SPSS, Inc., Chicago, IL). Mean values are presented with their standard deviations. We assessed mean differences in the linear measurements and volume of the PCF for 50 patients and 50 control subjects using independent-sample Student's t tests. Significance was indicated by a two-tailed P value of less than 0.05. For 50 patients, morphometric features of the PCF were compared with clinical disability (as measured by Karnofsky scores) using univariate correlations and a stepwise multiple logistic regression model, to identify potential radiographic variables affecting outcomes. In the study population, the extent of tonsillar descent was compared with Karnofsky scores and the incidence of syringomyelia using univariate logistic regression analysis.

RESULTS ⊡
Clinical presentation ⊡

Table 1 shows variations in the clinical presentation of CMI. There were 275 female and 89 male patients, with a mean age of 35.9 +/- 16.8 years (range, 1-76 yr). The age of onset was defined as the time when the patient first sought medical attention. One hundred thirty-four patients (37%) reported histories of lifelong complaints such as headaches and clumsiness. Patients with syringomyelia presented at a slightly younger age (24.7 +/- 16.6 yr) and received diagnoses earlier (30.3 +/- 16.2 yr) than did patients without syringomyelia (25.2 +/- 14.2 and 31.7 +/- 14.7 yr, respectively). Although the majority of patients described a spontaneous onset of symptoms, 89 (24%) cited trauma as the precipitating event. Common misdiagnoses included

migraine, fibromyalgia, and multiple sclerosis. By the time of definitive diagnosis, 215 patients (59%) had been told by at least one physician that they suffered from a psychogenic disorder.

Clinical syndrome

The most common symptom of CMI was suboccipital headache. This was experienced by 296 patients (81%) and was described as a heavy, crushing, or pressure-like sensation at the back of the head that radiated to the vertex and behind the eyes and inferiorly to the neck and shoulders. The headaches had a pounding quality when severe but were otherwise nonthrobbing. A distinctive feature of the headaches was their tendency to be accentuated by physical exertion, Valsalva maneuvers, head dependency, and sudden changes in posture. Female patients of menstrual age tended to experience an accentuation of symptoms during the week preceding menses. With few exceptions, Chiari-related headaches could be clearly distinguished from cervicogenic and other headache syndromes.

Ocular disturbances were reported by 283 patients (78%) (Table 2). Affected individuals were defined as those with two or more of the following intermittent symptoms: retro-orbital pressure or pain, visual phenomena such as floaters or flashing lights, blurred vision, photophobia, diplopia, and visual field cuts. Most of these symptoms were accentuated by the same factors that affected suboccipital headaches. Neuroophthalmological examinations revealed few objective findings. Ocular disturbances among young women were the leading cause of erroneous diagnoses of multiple sclerosis.

Symptoms and Signs	No. of Patients		
	CMI (n = 126)	CMI/SM (n = 238)	All Patients (n = 364)
Subjective			
Retro-orbital pressure or pain	80	150	230
Visual phenomena[b]	74	126	200
Blurred vision	62	111	173
Photophobia	36	67	103
Diplopia	28	43	71
Field cuts	7	17	24
Other[c]	8	15	23
Neuro-ophthalmological findings			
Impaired visual acuity	11	23	34
Extraocular muscle palsy	6	11	17
Papilledema	2	7	9
Field cuts	0	0	0
Affected patients[d]	97	186	283

[a] CMI, Chiari I malformation; SM, syringomyelia.
[b] Includes floaters, wavy lines, flashing lights, and visual blackout.
[c] Includes excessive tearing, eyelid twitching, and hyperemia of the conjunctiva.
[d] Affected patients were defined as those with two or more symptoms.

TABLE 2. Ocular Disturbances in Patients with the Chiari I Malformation[a]

A total of 269 patients (74%) experienced otoneurological disturbances that included two or more of the following symptoms: dizziness, disequilibrium, pressure in the ears, tinnitus, decreased hearing or hyperacusis, vertigo, and oscillopsia (Table 3). Like ocular disturbances, most of these symptoms were accentuated by the same factors that affected suboccipital headaches. There were very few objective findings except for nystagmus. Complete otological examinations were performed for 24 patients with disabling dizziness or vertigo. For 16 patients, audiometric testing revealed low-frequency sensorineural hearing loss in association with two types of vestibulopathy, i.e., a peripheral type characterized by impaired caloric responses and the absence of central abnormalities (12 patients) and a central type characterized by normal caloric responses and distinct neural abnormalities, such as impaired opticokinetic nystagmus, impaired smooth pursuit, saccadic dysmetria, and downbeat, positional, or periodic alternating nystagmus (2 patients).

Symptoms and Signs	No. of Patients		
	CMI (n = 126)	CMI/SM (n = 238)	All Patients (n = 364)
Subjective			
Dizziness	72	136	208
Disequilibrium	71	118	189
Pressure in ears	61	105	166
Tinnitus	56	84	140
Decreased hearing	44	88	132
Vertigo	22	49	71
Oscillopsia	17	32	49
Hyperacusis	8	17	25
Nystagmus			
Lateral	22	41	63
Downbeat	8	15	23
Rotary	2	8	10
Complete otological examination (n = 24)[b]			
Audiometric testing			
Sensorineural hearing loss	10/15	6/9	16/24
Conductive loss	0/15	0/9	0/24
Normal	5/15	3/9	8/24
Vestibular function testing			
Peripheral abnormalities	9/15	3/9	12/24
Central abnormalities	1/15	1/9	2/24
Normal	5/15	5/9	10/24
Affected patients[c]	89	180	269

[a] CMI, Chiari I malformation; SM, syringomyelia.
[b] Includes 24 patients with disabling dizziness or vertigo.
[c] Affected patients were defined as those with two or more symptoms.

TABLE 3. Otoneurological Disturbances in Patients with the Chiari I Malformation[a]

Table 4 summarizes lower cranial nerve, brain stem, and cerebellar disturbances for 191 patients (52%). The most common symptoms were dysphagia, sleep apnea, dysarthria, tremors, palpitations, and poor coordination. Objective findings consisted of cranial nerve deficits and cerebellar signs in a minority of the patients. The diagnosis of sleep apnea was confirmed for 30 patients by 24-hour sleep monitoring. For 28 of 42 patients with histories of palpitations or evidence of bradycardia in physical examinations, continuous cardiac monitoring demonstrated either paroxysmal atrial tachycardia (23 patients) or episodes of tachycardia and bradycardia (5 patients).

Symptoms and Signs	No. of Patients		
	CMI (n = 126)	CMI/SM (n = 238)[b]	All Patients (n = 364)
Subjective			
Dysphagia	57	100	157
Sleep apnea	41	99	140[c]
Dysarthria/hoarseness	42	71	113
Tremors	31	65	96
Palpitations	28	65	93[d]
Poor coordination	25	60	85
Throat pain	12	48	60
Facial pain or numbness	7	50	57
Syncope	12	34	46
Shortness of breath	9	25	34
Hypertension	7	21	28
Neurological abnormalities			
Impaired gag reflex (CN IX)	17	44	61
Tremors	16	39	55
Dysmetria	5	22	27
Facial sensory loss (CN V)	5	20	25
Vocal cord paralysis (CN X)	6	18	24
Truncal ataxia	3	9	12
Other[e]	3	14	17
Affected patients[f]	69	122	191

[a] CMI, Chiari I malformation; SM, syringomyelia; CN, cranial nerve.
[b] Includes 21 patients with syringobulbia.
[c] Confirmed for 30 patients by 24-hour sleep monitoring.
[d] Includes 23 patients with paroxysmal atrial tachycardia and 5 patients with episodes of tachycardia and bradycardia demonstrated by continuous cardiac monitoring.
[e] Includes deficits of Cranial Nerves XII (10 patients), VII (5 patients), and XI (2 patients).
[f] Affected patients were defined as those with two or more symptoms.

TABLE 4. Lower Cranial Nerve, Brain Stem, and Cerebellar Disturbances in Patients with the Chiari I Malformation[a]

Disturbances of spinal cord function were present in 223 of 238 patients (94%) with syringomyelia (Table 5). The incidence, type, and severity of symptoms were typical for syringomyelia (12,18,32,36,50,63,64,78). An unexpected finding was the presence of similar but less severe disturbances in 83 of 126 patients (66%) without syringomyelia. In this group, the most common symptoms were muscular weakness, paresthesia or hyperesthesia, nonradicular segmental pain, analgesia or anesthesia, spasticity, trophic phenomena, burning dysesthesia, and poor position sense. Objective findings included impaired fine-motor function of the hands (48 patients), muscular weakness (25 patients), analgesia or anesthesia (18 patients), and hyperreflexia (18 patients). Nonspecific disturbances in the study population included chronic fatigue (210 patients), impaired recent memory (142 patients), cervicogenic pain (125 patients), low back pain (87 patients), and episodic nausea or vomiting (65 patients).

Symptoms and Signs	No. of Patients		
	CMI (n = 126)	CMI/SM (n = 238)	All Patients (n = 364)
Subjective			
Sensory			
Paresthesia/hyperesthesia	40	175	215
Nonradicular segmental pain	29	131	160
Analgesia or anesthesia	24	123	147
Burning dysesthesia	15	91	106
Poor position sense	11	71	82
Impaired temperature sensation	3	78	81
Motor			
Muscular weakness	51	157	208
Spasticity	16	93	109
Muscular atrophy	3	28	31
Trophic phenomena[b]	15	57	72
Urinary incontinence	9	53	62
Impotence (75 adult male patients)	3/24	15/51	18/75
Fecal incontinence	0	7	7
Objective			
Sensory			
Analgesia or anesthesia	18	102	120
Dissociated sensory loss	0	72	72
Impaired position sense	5	59	64
Motor			
Muscular weakness	25	145	170
Impaired fine-motor function	48	113	161
Increased muscle tone	8	61	69
Muscular atrophy	1	25	26
Reflexes			
Hyperreflexia	18	107	125
Clonus or Babinski sign	7	57	64
Hyporeflexia	1	59	60
Trophic abnormalities	4	32	36
Affected patients[c]	83	223	306

[a] CMI, Chiari I malformation; SM, syringomyelia.

TABLE 5. Spinal Cord Disturbances in Patients with the Chiari I Malformation[a]

MRI findings ±|

Table 6 summarizes the MRI features of CMI. The most constant findings were compression of the CSF spaces posterior and lateral to the cerebellum (364 patients), tonsillar herniation of at least 5 mm (332 patients), reduced height of the supraocciput (306 patients), and increased slope of the tentorium (298 patients). Other findings included reduced length of the clivus, anterior displacement of the cerebellum, kinking of the medulla, retroflexion of the odontoid process, basilar invagination, compression of the fourth ventricle, empty sella, hydrocephalus, and syringobulbia. Minimal evidence of hindbrain overcrowding consisted of obliteration of the retrocerebellar CSF spaces in association with a meniscus sign at the lower pole of the cerebellar tonsils. For 47 of 364 patients who underwent phase-contrast CINE-MRI, including 21 patients with tonsillar herniation of less than 5 mm (Fig. 2), there was evidence of decreased CSF velocity/flow in the cisterna magna and subarachnoid space posterior to the cerebellum (47 patients) and the premedullary and prepontine spaces anterior to the brain stem (15 patients). Spinal abnormalities associated with CMI included syringomyelia (238 patients), scoliosis or kyphosis (152 patients), increased cervical lordosis (47 patients), and Klippel-Feil syndrome (18 patients). Of 32 patients with tonsillar herniation of less than 5 mm, 17 (53%) had syringomyelia.

Abnormalities	No. of Patients		
	CMI (n = 126)	CMI/SM (n = 238)	All Patients (n = 364)
Head MRI			
Compression of cerebellar cisterns	126	238	364
Tonsillar herniation of ≥5 mm	118	224	332
Reduced height of supraocciput	105	201	306
Increased slope of tentorium	103	195	298
Reduced length of clivus	64	116	180
Anterior displacement of cerebellum	58	97	155
Kinking of medulla	44	96	140
Retroflexion of odontoid process	38	58	96
Basilar invagination	12	32	44
Compression of fourth ventricle	14	30	44
Empty sella	12	25	37
Hydrocephalus	4	21	25
Syringobulbia	0	21	21
Other[b]	7	12	19
CINE-MRI measuring CSF velocity/flow at foramen magnum (47 patients)[c]			
Decreased posteriorly	22/22	25/25	47/47
Decreased anteriorly	7/22	8/25	15/47
Spine MRI			
SM	0	238	238
Scoliosis or kyphosis	35	117	152
Increased cervical lordosis	15	32	47
Klippel-Feil syndrome	4	14	18
Other[d]	7	20	27

[a] CMI, Chiari I malformation; SM, syringomyelia; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.
[b] Includes clivus segmentations, occipitalization of the atlas, and condylar hypoplasia.
[c] All studies consisted of midsagittal, two-dimensional, phase-contrast scans that were centered at the foramen magnum and calibrated for CSF. The data reflect CSF velocity and flow in two areas, i.e., the cisterna magna and subarachnoid space posterior to the cerebellum, and the premedullary and prepontine subarachnoid spaces anterior to the brain stem.
[d] Includes hemivertebra, os odontoideum, and congenital spinal stenosis but not degenerative disc disease.

TABLE 6. Magnetic Resonance Imaging Findings for Patients with the Chiari I Malformation[a]
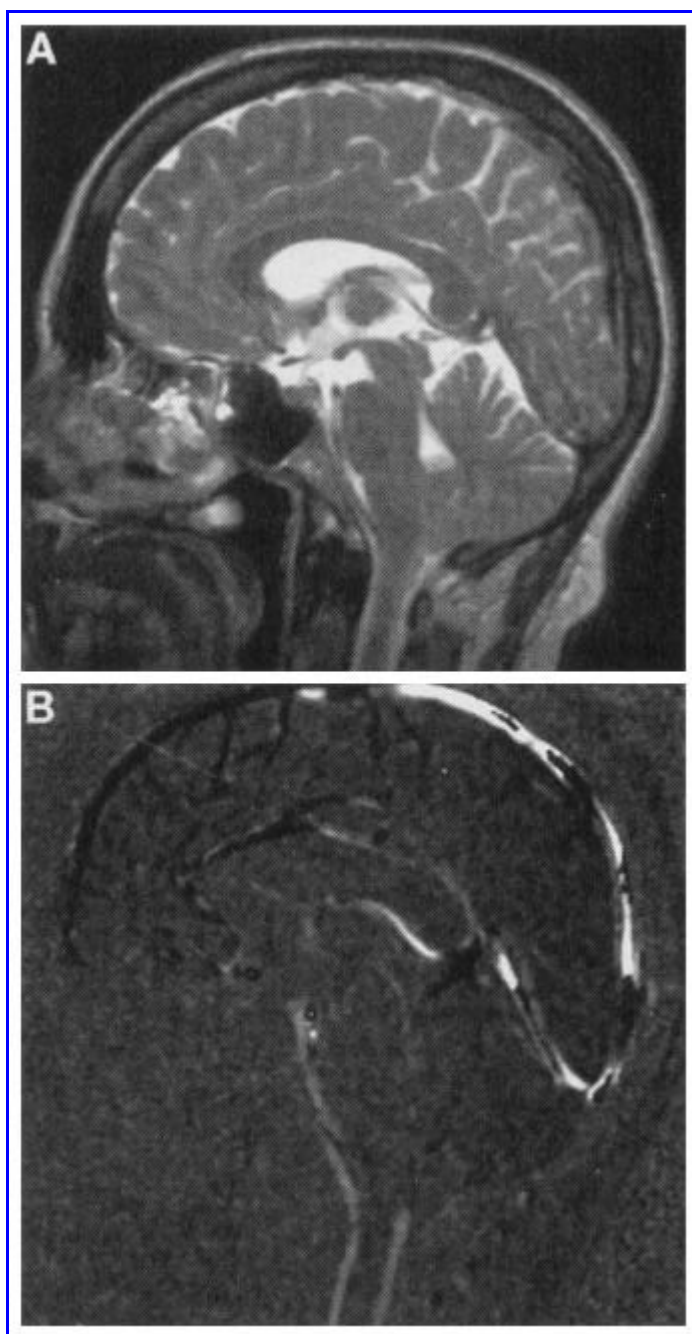
FIGURE 2. MRI findings for a 51-year-old female patient with tonsillar herniation of less than 5 mm and the following intractable symptoms: suboccipital headaches that were accentuated by exertion and Valsalva maneuvers; pseudotumor-like episodes of retro-orbital pain, visual phenomena, and blurred vision; Meniere's syndrome; dysphagia, hoarseness, and palpitations; and segmental sensory and motor complaints in the absence of syringomyelia. *A*, T2-weighted sagittal MRI scan, demonstrating tonsillar herniation of less than 5 mm. There is evidence of obliteration of the CSF spaces posterior to the cerebellum. Morphometric analysis of the PCF revealed a reduced volume of CSF (13.5 ml). *B*, CINE-MRI scan, showing reduced CSF velocity/flow in the subarachnoid space posterior to the cerebellum and cisterna magna. The patient experienced immediate relief of symptoms after PCF decompression.

Quantitative measurements of the PCF ⬆️

Table 7 compares linear and volumetric measurements of the PCF for 50 patients and 50 control subjects. For patients with CMI, the following statistically significant abnormalities were demonstrated: reduced mean height of the supraocciput ($P < 0.001$), reduced mean length of the clivus ($P < 0.001$), increased mean slope of the tentorium ($P < 0.001$), tonsillar herniation (mean

+/- standard deviation, 9.8 +/- 5.8 mm; $P < 0.001$), reduced mean total volume of the PCF ($P = 0.001$), and reduced mean CSF volume of the PCF ($P < 0.001$). There was no significant difference in the mean brain volume of the PCF ($P = 0.369$) in patients, compared with control subjects.

Variable	Control Subjects (n = 50)[b]	CMI (n = 50)[b]	P^c
Age (yr)	36.8 ± 20.9	37.8 ± 14.8	0.783
Gender (M/F)	17/33	13/37	0.388
Linear measurements (mm)			
Supraocciput	41.8 ± 5.2	37.7 ± 5.9	<0.001
Clivus	40.4 ± 5.1	36.6 ± 4.2	<0.001
Tentorial angle[d]	82.5 ± 7.2	90.0 ± 7.7	<0.001
Tonsillar descent	−2.1 ± 3.7	9.8 ± 5.8	<0.001
Volumetric measurements (ml)			
Total posterior fossa	137.9 ± 18.7	124.5 ± 21.4	0.001
Brain	111.9 ± 14.9	108.6 ± 21.4	0.369
CSF	26.7 ± 7.3	15.9 ± 7.1	<0.001

[a] CMI, Chiari I malformation; CSF, cerebrospinal fluid.
[b] Values are means ± standard deviations.
[c] P values are for comparisons between randomly selected patients and control subjects.
[d] Angle formed by the tentorium with a line drawn between the center of the inion and the opisthion.

TABLE 7. Quantitative Measurements of the Posterior Cranial Fossa in Patients with the Chiari I Malformation[a]

Clinicoradiological correlations

The Karnofsky score for patients who underwent quantitative measurements of the PCF was 72.2 +/- 10.8 (mean +/- standard deviation). No significant correlations were found between Karnofsky scores and the following radiographic variables: height of the supraocciput, length of the clivus, slope of the tentorium, extent of tonsillar descent, CSF volume of the PCF, and total volume of the PCF. In the study population of 364 patients, the extent of tonsillar descent was not correlated significantly with Karnofsky scores or the incidence of syringomyelia.

Familial incidence and inheritance patterns

Forty-three patients (12%) had at least one close relative with one of the following diagnoses: CMI and syringomyelia (19 families), CMI in the absence of syringomyelia (17 families), or syringomyelia of unknown origin (7 families). An additional 72 patients reported that at least one close relative exhibited symptoms similar to their own but had not been evaluated by neuroimaging. The only neural defect encountered among more than 4000 close relatives was meningomyelocele (two families), which is consistent with the incidence of this anomaly in the general population (24).

The pedigrees of 21 families with two or more affected members are shown in Figure 3. Affected female subjects (36 individuals) outnumbered affected male subjects (12 individuals) by 3:1. There were several types of familial recurrence, as follows: 1) parent-to-child, including two cases of apparent male-to-male transmission, 2) "transmission" through apparently unaffected relatives, and 3) recurrence in sibships. Two families included one pair of dizygotic twins concordant for CMI, and one family included one pair of monozygotic twins concordant for CMI; zygosity in same-gender twins was established with more than 99% accuracy using a panel of six highly polymorphic, microsatellite, repeat deoxyribonucleic acid markers. The pedigrees of 21 families showed patterns consistent with autosomal dominant inheritance (male-to-male transmission, vertical transmission) with reduced penetrance (transmission through apparently unaffected relatives) or autosomal recessive inheritance (neither parent affected). It is appropriate to point out that the occurrence of familial aggregation is also consistent with other interpretations, including common environmental exposures and random chance.
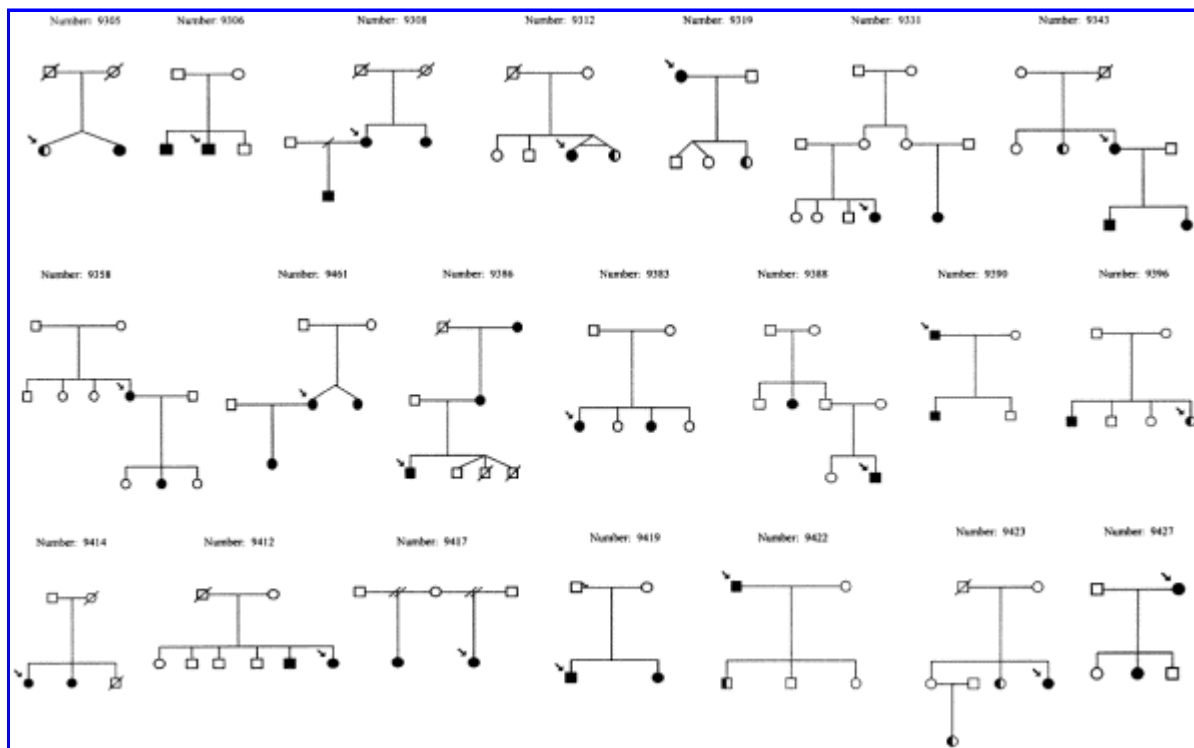

FIGURE 3. Pedigrees of 21 families with CMI affecting two or more members. *Circles*, female family members; *squares*, male family members; *black symbols*, affected family members; *white symbols*, unaffected family members; *symbols with a slash mark*, family members who have died; *arrows*, the consultants/probands; *angled lines*, dizygotic twins; *angled lines joined by a bar*, monozygotic twins; *slash marks between parents*, parents who have divorced.

DISCUSSION

Chiari malformations are generally regarded as a pathological continuum of increasingly severe hindbrain maldevelopments (12,32,78). The association of Chiari II and Chiari III malformations with embryological defects of the brain and spinal cord has established these lesions as primary neural anomalies (14,26,59). However, there is clinical and experimental evidence that chronic tonsillar herniation in CMI could be attributable to underdevelopment of the occipital bone and overcrowding of the cerebellum within a too-small PCF (10,35,54,55,71,72,86,96,102). Recent morphometric studies are consistent with this view (10,71,86,96,102), and Nishikawa et al. (71) suggested that the fundamental defect may involve underdevelopment of the occipital somites originating from the para-axial mesoderm.

The proposition that CMI is a disorder of mesodermal origin was supported by the following findings in this study: 1) neurological examinations and MRI scans of the brain and spinal cord of 364 patients failed to provide any evidence of neuroectodermal defects; 2) the neural abnormalities that were present (e.g., syringomyelia and hydrocephalus) were attributable to the secondary effects of chronic tonsillar herniation; 3) the incidence of neural anomalies among close relatives of affected individuals was similar to that in the general population; and 4) the MRI findings of reduced height of the supraocciput, increased slope of the tentorium, hypoplasia of the clivus, and osseus abnormalities at the craniovertebral junction were consistent with a defect of the para-axial mesoderm.

Other MRI findings provided substantial evidence of hindbrain overcrowding. The most constant abnormality was compression of the CSF spaces posterior and lateral to the cerebellum (364 patients, 100%). Tonsillar herniation of at least 5 mm below the foramen magnum was present in 332 patients (91%). Less constant findings of hindbrain overcrowding included anterior displacement of the cerebellum, kinking of the medulla occurring with retroflexion of the odontoid process or basilar invagination, and compression of the fourth ventricle. Quantitative measurements of the PCF demonstrated significant reductions in CSF volume ($P < 0.001$) and total PCF volume ($P = 0.001$) but no differences in brain volume ($P = 0.369$) for 50 randomly selected patients, compared with control subjects. Taken together, these findings support and extend accumulating evidence that the fundamental problem in CMI is a volumetrically small PCF (10,71,86,96,102), which results in varying degrees of hindbrain overcrowding. Similar abnormalities probably underlie the development of "acquired CMI" in some cases of craniosynostosis (27), hypophosphatemic rickets (22), achondroplasia (69), and Paget's disease (80).

There is limited information regarding the epidemiological features of CMI. The anomaly is defined as a rare disorder (70), and female subjects outnumber male subjects by a wide margin (50,71,78). As shown in Table 1, approximately 25% of patients cited trauma as the precipitating factor. The most common mechanisms were whiplash injuries and direct blows to the head and neck (53), which raises the possibility that certain types of trauma accentuate tonsillar impaction or result in subarachnoid hemorrhage that destabilizes a marginally compensated CSF system.

The likelihood that CMI can be genetically transmitted has been suggested by two lines of evidence, i.e., the association of CMI with known genetic disorders, such as achondroplasia (69), Hadju-Cheney syndrome (99), and Klippel-Feil syndrome (71,101), and case reports of familial aggregation (9,23,39,59), including cases of monozygotic twins (9,92) and triplets (23) concordant for CMI. The incidence of familial syringomyelia is reported as 2% (25), but there are no data, to our knowledge, regarding the risk of inheritance in CMI. In this study, 43 patients (12%) reported positive family histories for CMI or syringomyelia. Analysis of the pedigrees of 21 families revealed patterns of inheritance consistent with autosomal dominant inheritance with reduced penetrance or autosomal recessive inheritance. These modes of transmission have also

been reported for patients with familial syringomyelia (16,21,109).

Previous reports have documented the complex symptom patterns for CMI (12,18,20,31,32,35,50,78,89,95,107). Presenting symptoms can include headaches (47,56,75-77,93,98,100) in association with a wide variety of ocular (3,51,56,85,90,97,108), otoneurological (15,38,41,44,48,52,68,84,85,87,103,105), brain stem (2,5-7,19,29,30,34,43,46,49,57,79,83,97,104), and spinal cord (29,36,62,64) disturbances. Although many of the symptoms discussed in this report (Tables 2-5) have been described previously, some are less familiar or have been difficult to relate to the specific effects of tonsillar herniation and syringomyelia. A majority of the patients in the study population complained that their symptoms had been ascribed to psychogenic causes.

There is evidence that some ambiguous or unfamiliar symptoms may be CSF-related. For example, given the significant reduction of CSF volume in the PCF demonstrated in this study (mean, 10.8 ml; 40%), it is evident that newly formed CSF is displaced from the compressed subarachnoid spaces of the PCF into available spaces within the supratentorial and spinal compartments. Such displacements almost certainly affect CSF compliance and would be expected to alter the normal damping effect of an open CSF system, which mitigates changes in venous volume and pressure occurring with respirations, the cardiac pulse, Valsalva maneuvers, and changes in posture (60). Under these conditions, CSF displacements could play a role in the following symptoms: 1) sub-occipital headaches that radiate to the vertex and behind the eyes and inferiorly to the neck and shoulders, 2) pseudotumor-like episodes of retro-orbital pain and visual phenomena, and 3) a Meniere's disease-like syndrome of pressure in the ears, dizziness, disequilibrium, tinnitus, and hearing loss. The exquisite sensitivity of these symptoms to physical activities, including Valsalva maneuvers, is consistent with reduced compliance of the CSF system. For some patients with vestibular dysfunction, otological testing revealed low-frequency sensorineural hearing loss in association with peripheral vestibulopathy (Table 3). These findings fulfill the criteria for endolymphatic hydrops (4,42) and suggest that CSF displacements in CMI contribute to disturbances of CSF-perilymph dynamics.

The most obvious CSF-related symptoms are those attributable to syringomyelia (Table 5). These can occur because of stretching and distention of nervous tissue or dissection of central canal cavities into the parenchymal tissues of the spinal cord (61). Although it was once thought that syringomyelia was caused by the forceful diversion of CSF from the fourth ventricle into the central canal (37,106), it is now known that most syrinxes do not communicate with the fourth ventricle and are separated from it by an occluded or stenotic segment of the canal (61,63,65). Current evidence suggests that syrinx formation is the result of an obstruction of CSF flow at the foramen magnum, which exaggerates the pulsatile systolic pulse wave in the spinal subarachnoid space (73) and drives CSF through anatomically continuous perivascular and interstitial spaces (66,67,91) into the central canal of the spinal cord. More severe obstructions of CSF circulation are occasionally causes of hydrocephalus (Table 6).

An unexpected finding in this study was the presence of spinal cord disturbances in 83 of 126 patients (66%) who did not have syringomyelia. Some of these disturbances are related to mechanical compression of the cervicomedullary junction (12,18,29,32,78), but another explanation could be that the exaggerated systolic pulse wave in the spinal canal is capable of producing symptoms that mimic those of syringomyelia. Compression of the brain stem and lower cranial nerves was the most likely cause of dysphagia, hoarseness, sleep apnea, and palpitations. The incidence of cardiac irregularities in the study population seemed unusually high for a cohort of predominantly young adult female subjects, and an association between sinus arrhythmia and CMI was noted previously (43,88,97). It is acknowledged that many of the symptoms described in this report occur with variable frequencies in the general population and could be unrelated.

Clinical descriptions of CMI have undergone continuous revision since the original report, by Chiari (26), of tonsillar herniation in patients dying as a result of hydrocephalus. In recent years, the term CMI has been used synonymously with tonsillar ectopia or chronic tonsillar herniation in a wide variety of congenital and acquired disorders. The radiological definition of CMI has been reported as tonsillar herniation of at least 3 mm (13) or at least 5 mm (1) below the foramen magnum. However, this definition is limited to a single criterion and makes no reference to clinical symptoms or the presence or absence of associated findings such as syringomyelia.

The radiological definition of CMI may be too restrictive. In this study, there were 32 of 364 patients (9%) who exhibited tonsillar herniation of less than 5 mm and symptoms that were typical of CMI. Seventeen of those 32 patients (53%) had syringomyelia. All patients showed MRI evidence of hindbrain overcrowding (Fig. 2A), and CINE-MRI demonstrated abnormalities of CSF velocity/flow (Fig. 2B) that were similar to those reported for patients with tonsillar herniation of at least 5 mm (8,17,81). These observations indicate that the extent of tonsillar herniation cannot be used as the sole criterion for the diagnosis of CMI. We could not confirm reports (1,11,33,94) that the severity of symptoms is directly related to the extent of tonsillar herniation. Because tonsillar herniation of at least 5 mm can be encountered as an incidental finding among asymptomatic patients (33), it is likely that the position of the cerebellar tonsils, although providing a general index of hindbrain overcrowding, is only one factor influencing the clinical features of CMI.

CONCLUSIONS ±

CMI is a disorder of the mesoderm and is thus inherently different from Chiari II and Chiari III malformations. The anomaly occurs sporadically but can be transmitted genetically in some families. The most constant feature of CMI is a volumetrically small PCF, which predisposes patients to hindbrain overcrowding. Displacements of CSF probably contribute to the symptoms. The clinical syndrome of CMI is characterized by headaches, pseudotumor-like episodes, a Meniere's disease-like syndrome, lower cranial nerve signs, and spinal cord disturbances even in the absence of syringomyelia. Diagnosis is established by MRI. Minimal evidence of hindbrain overcrowding consists of obliteration of the retrocerebellar CSF spaces in association with a meniscus sign at the lower pole of the cerebellar tonsils. CINE-MRI can be helpful in demonstrating a disturbance of CSF velocity/flow at the foramen magnum in patients with tonsillar herniation of less than 5 mm.

ACKNOWLEDGMENTS ±

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