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SPECIAL ANNUAL ISSUE

Clinical diagnosis—part II: what is attributed to Chiari I

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Abstract

Purpose Chiari malformation type I is identified as radiological appearance of cerebellar tonsil herniation below the foramen magnum. The wide spectrum of clinical manifestations variably associated sometimes encompasses signs and symptoms whose correlation with the malformation remains debatable. However, a correct clinical framework is relevant in tailoring the strategy of management, and in particular, establishing the appropriate surgical intervention.

Methods An analysis of relevant articles on this issue was performed, involving both single case reports and case series. The papers were obtained from electronic databases including PubMed/MEDLINE and Google Scholar, as well as direct contact with some authors.

Results This review focuses on those unusual clinical pictures attributed to Chiari malformation type I (CMI), investigating their actual relationship with the morphological condition. Supposed physiopathogenetic mechanisms and clinical relevance are discussed along with an analysis on the surgical indications and results.

Conclusion There is no clear explanation on why some patients may exhibit uncommon symptoms, often in association with the most frequent ones, but even reported as single initial clinical occurrence. Their actual incidence may have been roughly underestimated in the literature so far, because of wide heterogeneity of selection and analysis among different studies.

Most of the authors appear sharing the impression that CMI surgical decompression plays a significant role in controlling the majority of these unusual symptoms, stressing their actual occurrence in relation with the malformation. A routinely multidisciplinary clinical approach has become advisable to encompass the diversity of conditions potentially associated with CMI and improve the care of CMI patients.

Keywords Chiari malformation type I · Multisystem manifestations · Unusual symptoms · Foramen magnum decompression

Introduction

The definition of Chiari malformation type I (CMI) is based on a morphological description, related to anatomo-radiological characteristics. The broad spectrum of clinical manifestations variably associated sometimes encompasses signs and symptoms whose correlation with the malformation remains debatable. Moreover, the symptoms' presentation of CMI varied by age and the possibly associated diseases or syndromes [53]. This is all the more true since an increasing number of cases have been depicted due to the easier availability of magnetic resonance imaging (MRI) performed for different reasons.

Physicians, and in particular neurosurgeons, are therefore facing increasingly a wider constellation of clinical features which may have improved the clinical characterization of CMI patients than in the past, but such an amount of information actually can result rather confusing and dispersive (Table 1) [17, 53]. However, a correct clinical framework is relevant in tailoring the strategy of management and in particular, establishing the appropriate surgical intervention.

The aim of this review is to explore those clinical pictures attributed to CMI, according to a large pool of case reports and case series reported in recent years, investigating their actual relationship with the morphological condition. Supposed physiopathogenetic mechanisms and clinical relevance are discussed along with an analysis on the surgical indications and results.

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Table 1 Summary of the uncommon symptoms and signs associated with CMI reported in the literature

Synopsis of uncommon symptoms and signs associated with CMI			
	Supposed anatomical causes	Symptoms	Signs
Ocular manifestations	II nerve impairment	Blurred vision photophobia visual phenomena	Papilloedema
	VI nerve/nucleus paralysis (uni- or bilateral)	Diplopia	Convergent strabismus
	Ocular movement disorders	Oscillopsia	Gaze-evoked nystagmus (with shifted null position) Downbeat nystagmus periodic alternating nystagmus Convergence nystagmus Skew deviation Ocular flatter Ocular dysmetria Spasm of the near reflex
Trigeminal neuropathy	V nerve/nucleus neuropathy (uni- or bilateral)	Facial ache (one or more branches) Triggerable sudden intense lancinating	
Facial neuropathy	VII nerve/nucleus palsy	Hemifacial spasm	Hemifacial spasm
Otoneurological disturbances	VIII nerve/nucleus palsy	Instability Vertigo Tinnitus Aural fullness Hyperacusis Hearing loss	Sensorineural deafness or loss of higher frequency component
Oropharyngeal dysfunction	IX and X nerves/nucleus palsy	Hiccups Cough Stridor Hoarseness of voice Gastroesophageal reflux Dysphonia Dysphagia Glossopharyngeal neuralgia	Reduced gag reflex Vocal cord paralysis with, recurrent aspiration (respiratory infections) Palatal weakness Tongue atrophy Cricopharyngeal achalasia Poor weight gain Failure to thrive
Cardiovascular impairments	X nerves/nucleus palsy	Syncope Palpitations	Sinus bradycardia Postural tachycardia Arterial hypertension
Sleep-related breathing disorders (SRBD)	Pontine respiratory group in the brainstem Ventral respiratory group in medulla oblongata Dorsal respiratory group in the nucleus of the solitary tract IX and X cranial nerves	Drowsiness Snoring Sleep fragmentation REM parasomnias Insomnia	Central sleep apnea (CSAS) Obstructive sleep apnea (OSAS) Mixed forms (MSA)
Epilepsy	Cortical microdysgenesis	Focal onset (with prevalent complex partial semiology), with rare secondary generalization	
Cognitive impairment	Flocculonodular lobe connections with the prefrontal cortex	Brain fog Disruption in concentration	Impairment in executive function, attention Working memory Visuospatial skills Perceptual skills Language development (mainly in pediatric)
Behavioral disorders	Locus coeruleus	Anxiety Depression Panic Dysphoria Irritability Aggression Ruminative behaviors Obsessive behaviors	Difficulty in processing emotional content

Ocular manifestations

Ocular disorders associated with CMI are relatively uncommon [62]. They may include a wide variety of symptoms and signs, encompassing subjective disturbs as impaired visual acuity and/or field (blurred vision, photophobia, oscillopsia, visual phenomena), and objectively documented oculomotor and abducens nerve palsy (diplopia) [2, 53]. As well, a variety of eye movement deficits with different forms of nystagmus (periodic alternating, downbeat, see-saw, convergence nystagmus), skew deviation, ocular flatter, ocular dysmetria, and spasm of the near reflex have been reported so far [2, 69]. However, eye movement deficits are not commonly used as clinical markers for establishing CMI diagnosis or tailoring the impact of treatment [69].

Papilloedema

Papilloedema represents one of the most scaring signs [72]. Indeed, its presence has traditionally been related with increased intracranial pressure (ICP), namely in idiopathic intracranial hypertension (IIH), a condition requiring prompt intervention to control the risk of permanent visual loss. It is rarely described in association with Chiari I malformation (CIM), previously reported in a 2% of patients with symptomatic CIM [55]. However, most of the literature on this argument is based on anecdotal observations [65]. A craniospinal CSF pressure unbalance is supposed to be the underlying physiopathogenetic mechanism of intermittent elevated ICP in these cases, caused by obstruction of the CSF flow at the level of the foramen magnum, which, in its turn, alters the normal damping effect of an open system able to accommodate venous and pressure changes occurring during breathing, cardiac pulse, Valsalva maneuver, and change in posture [65]. Other signs related to raised ICP include tortuosity of the optic nerve, flattening of the posterior sclera, and intraocular protrusion of the prelaminar optic nerve; they all have been seldom described in the presence of CIM [6]. The measurement of the optic nerve sheath diameter (often used as non-invasive method of ICP assessment) did not prove a sufficient specificity to be included as a routinely evaluation in early accurate diagnosis of CIM requiring prompt surgical intervention [6].

On this ground, some authors suggested the use of dynamic MRI CSF flow study to differentiate between Chiari I malformation with papilledema and IIH to tailor the correct surgical management [79]. Indeed, the indication of posterior fossa decompression for papilledema associated with CIM remains controversial since literature describes only sporadic case reports on papilledema improvement after CIM surgery, as well as resolution of this symptom after acetazolamide therapy [72].

Abducens nerve paralysis

Sixth nerve palsies associated with CMI have been described in the literature mainly as case reports [51, 62, 64]. It has been reported either in monolateral or in bilateral appearance, variably associated with facial weakness [51, 62, 64]; it often occurs in association with other typical clinical signs and symptoms, but sporadic isolated forms of comitant strabismus have been depicted as well [64].

Indeed, Chiari malformation rarely presents with its involvement, despite the delicate neuroanatomical architecture of the cerebellopontine angle predisposes the abducens nerve deficit in several tumoral and/or traumatic lesions occurring in this region. The VI cranial nerve courses through the prepontine cistern running upwards to Dorello's canal, which makes it particularly prone to the ischemic effect of tractional forces occurring due to the caudal displacement of the cerebellum [62], as described in the setting of lumbo-peritoneal shunts, posterior fossa tumors, and birth trauma. These patients, more frequently in the acute forms of presentation, can exhibit the coexistence of syringobulbia and/or syringomyelia on MRI [52].

Posterior fossa decompression is currently recommended as first surgical procedure in these circumstances, preceding strabismus surgery, which must be delayed 6 to 9 months after neurosurgical decompression, since the deviation may improve partially or completely after 5 months on average [64]. On the contrary, the direct surgical repair of esotropia is associated with a higher incidence of recurrence (success rate, 30% after this surgical procedure) and appearance of downbeat nystagmus [69].

Nystagmus

This is the most common eye movement disorder reported in the literature, with 27–60% of cases noting an acquired nystagmus [62]. Several types of nystagmus have been described in association with CMI in variable proportions, including gaze-evoked nystagmus, with shifted null position, downbeat nystagmus, and periodic alternating nystagmus [69]. Different pathways of the oculomotor and vestibulo-ocular system are involved for each type of nystagmus.

The gaze-evoked nystagmus represents the most common form, described in up to 30% of patients [69]. Horizontal eye movements are regulated by the oculomotor neural integrator, driven by the brainstem, in particular by the medial vestibular nucleus and the nucleus prepositus hypoglossi for the horizontal saccades and the interstitial nucleus of Cajal for the vertical and torsional saccades [69]. The cerebellar flocculus and parafloccculus interfere significantly with the neural integrator, and their damage causes slow phase of nystagmus and impaired ability to pursuit smoothly moving target. This is often seen in diffuse or focal cerebellar lesions. The gaze-evoked

nystagmus with shifted null position has been described in CMI patients, when asymmetric compression of the brainstem has been depicted [30].

The cerebellar flocculus is implicated as well in inhibiting the neuronal pathway projecting from the anterior semicircular canal to the vestibular nucleus and therefore to the extraocular motor neurons, driving upward eye movements. Its impairment produces downbeat nystagmus, which has been reported in a smaller proportion of patients with CMI (4–6%) [69].

Periodic alternating nystagmus is a spontaneous jerk horizontal nystagmus in the central gaze that reverses periodically every 90–120 s. It is often associated with lesions of the uvula and nodulus of the posterior cerebellar vermis, which exert a direct inhibitory control, via GABA release, on the velocity storage (time course of eye movements in response to vestibular and optokinetic stimulation) [2, 69].

Data from the literature report contradictory post-operative results: posterior fossa decompression in CMI tended to improve mainly the severity of downbeat nystagmus, and oscillopsia for nystagmus presented a less favorable outcome in some studies, whereas others showed a remarkable resolution of 75–100% even after decompression without tonsillectomy [32, 48, 69]. On the contrary, some authors investigated the occurrence of post-operative oculomotor dysfunction after neurosurgical suboccipital decompression, revealing that almost half of the patients experienced such complication, however mainly asymptomatic [32].

Trigeminal neuropathy

The association between trigeminal neuralgia and CMI is a not common, but well-known entity, even though there are mainly case reports described in the literature [31, 49, 50, 60, 74, 75, 80]. Some authors believe that its occurrence may be greater than actually reported so far [33]. The prevalence rate of patients with trigeminal neuralgia over CMI cases has been estimated at approximately 5–10% over a series of cases by a single-center experience [33].

Nevertheless, the first description in the literature dates back to the observations made by Dandy in 1934, when he described two cases in which trigeminal neuralgia was associated with congenital malformations at the base of the cranium, resembling a CMI, over a series of 215 patients who underwent posterior fossa decompression for section of trigeminal nerve [61].

The typical facial ache, limited to the distribution of one or more branches of the trigeminal nerve, with a characteristic of triggerable, sudden, intense, lancinating pain can manifest in unilateral or bilateral form, in association or not with several other symptoms, usually related with CMI, namely, occipital headache, weakness, sensory disturbance, and so on [33]. The radiological exams have not depicted a particular appearance in all the cases described, since tonsillar herniation, syringomyelia, and hydrocephalus were present in variable combination in all the cases reported [31, 49, 50, 61, 75, 76, 80].

Several theories have been postulated on the base of these anecdotic reports. Papanastassiou et al. [61] described at least four possible mechanisms: (a) vascular compression at the level of the nerve root entry zone, exacerbated by hydrocephalus or anatomic factors such as small posterior fossa; (b) stretching or elongation of the trigeminal nerve, causing a demyelination/remyelination phenomena; (c) microvascular insults, with microischemic injuries; and (d) direct brainstem compression, for limited volume of the posterior fossa and platybasia [70].

According to Gonzalez-Bonet et al. [33], the reason could be much easier: they stated that the posterior compression by the herniated tonsils in CMI may easily induce a direct damage, given the particular vulnerability of trigeminal nucleus fibers at the spinal tract (until C2 level) because of their low myelin and dorsal localization.

Interestingly, all the patients, who underwent posterior fossa decompression, experienced complete recover from facial pain, either initially presented as unilateral or bilateral forms. Even more interestingly, the direct treatment of hydrocephalus associated with CMI, prior to an eventual posterior fossa decompression, by means of either endoscopic third-ventriculostomy or ventriculoperitoneal shunt resulted to be effective in controlling symptoms [31, 75].

Facial neuropathy

Hemifacial spasm (HFS) is characterized by chronic, involuntary paroxysmal contractions involving the muscles on one side of the face [49]. It is generally classified by the Cohen and Albert grading system, which goes from grade I to IV according to the entity of spasm and daily life impairment [47].

The association between HFS and CMI is extremely rare, and only eight studies addressed this issue during the last three decades, reaching a total amount of 51 cases described so far [9, 15, 23, 43, 47, 49, 56, 16] (Table 2). The largest case number series of this association was published by two different authors with a high expertise in the treatment of HFS in 2017 [15, 47]. They evaluated the prevalence of CMI over a wide series of patients affected by HFS, stating a range from 1.9% (13 out of 675) to 3.4% (28 out of 831) (respectively, Li et al. and Cheng et al.) [15, 47]. Although these studies were biased by several factors, namely, retrospective nature of the analysis, the small number of cases each, and the fact that all the patients were referred exclusively for surgical treatment, interesting data were pointed out in their analysis in comparison with previously published case reports.

The clinical endowment does not differ significantly from the typical form of primary HFS, including female and left

Table 2 Summary of the cases reported in the literature on patients affected by CMI and HFS. Modified by Cheng et al. *BTX-A*, botulinum toxin type A; *FMD*, foramen magnum decompression; *MVD*, microvascular decompression; *VPS*, ventriculoperitoneal shunt

Authors/year	Number of pts	Age/sex	Treatment	Outcome
Leal-Filho et al. 1992	1	50/F	FMD	Improved
Braca et al. 2005	1	37/M	FMD + MVD	Resolved
Colpan et al.2005	1	18/M	FMD	Resolved
Felicio et al. 2007	5	Mean age 39.8 years F/M ratio 3:2	BTX-A 3 Drugs 2	60% improved
Mukerji et al. 2010	1	39/M	FMD	Resolved
Liu et al. 2014	1	24/M	VPS	Resolved
Li et al. 2017	13	Mean age 44.8 years F/M 8/5	MVD	85% resolved
Cheng et al. 2017	28	Mean age 36.4 years F/M 19/9	MVD 20 MVD + BTX-A 3 FMD 4 FMD + VPS 1	MVD group 91.3% resolved FMD group 60% resolved 40% improved

side preponderance and long disease duration, with the upper part of the face prevalently involved at onset [15, 47]. However, Cheng et al. [15] observed that in their series, the age at onset was significantly lower than that in patients with idiopathic HFS, maybe related to the prevalence of CMI detection on MRI in younger population. Indeed, only a minority of their patients showed CMI-related symptoms at admission, which influenced dramatically the choice of the surgical approach.

In this regard, the knowledge of the underlying physiopathological mechanism would tailor the surgical treatment properly. Several hypotheses have been postulated, without univocal explanation. They include a crowdedness of posterior fossa and the cerebellopontine angle (CPA) cistern inducing a direct compression on the nerve or favoring its contact with vascular structures, the abnormal CSF flow dynamics caused at the craniocervical junction responsible for traction of the nerve or further microischemic injuries [14, 15].

Among all the 51 patients reported in the literature, 36 underwent purely microvascular decompression (MVD) and only 9 posterior fossa decompression (of whom 2 had also MVD and MVD + VPS, respectively). The remaining 6 underwent botulinum toxin type A injection in 5 cases and VPS in the last one.

Microvascular decompression alone succeeded in relieving HFS in most patients at long-term follow-up (> 90% of cases). However, the recurrence rate in the long term was 14.3%, significantly higher than the one estimated for idiopathic HFS [15]. No information has been collected with concern to the evolution of CMI symptoms in previously asymptomatic patients, who had MVD for HFS.

Posterior fossa decompression was performed mainly when HSF coexisted with CMI-related symptoms: in such cases, HFS resolved or significantly improved in all the patients, along with the majority of CMI symptoms [15]. In these cases, the relief at craniocervical junction may have been sufficient to allow a relaxation of nervous structures, reducing the contact between the vessel and the facial nerve.

Otoneurological disturbances

Otolaryngologic manifestations in CMI are not so unusual, according to several reports (mainly case reports and case series) collected in the literature since the last four decades [36–38, 45, 58]. Levo et al. reported that the prevalence of CMI in their otologic patients seen in 2005 was 0.9% [45].

However, the characterization of the audiovestibular symptoms varied significantly from each single study and the quality of the observation results insufficient, preventing a univocal interpretation of the data because of a preponderant neurological/neurosurgical point of view in this paper.

Guerra Jimenez et al. [36] carried out an extensive literature review on this issue adding their personal experience over a series of 9 patients. They found that audiovestibular symptoms usually begin insidiously and progressively in the second and third decade of life, variably associated with typical CMI symptoms. The list of symptoms includes instability (49%), which is the most frequent, followed by vertigo in 18%, nystagmus (15%), hearing loss (15%), tinnitus (11%), aural fullness (10%), and hyperacusis (1%) [36, 58].

The vertigo is often defined as atypical positional and/or triggered by head movements [45]. Hearing loss appeared more prevalent in bilateral occurrence than in the unilateral

form [36]. CMI patients presented a higher median value of the amplitude ratio between potentials V and I on auditory-evoked potentials, suggesting a higher frequency of peripheral injuries of the auditory pathways, namely, the cochlear nerve (sensorineural deafness or loss of higher frequency component) [37].

Several theories have been proposed to explain the occurrence of hearing loss in CMI patients: the attention is focused on the already known possible mechanisms of stretching of the eighth cranial nerve by brainstem herniation, direct compression of the eighth cranial nerve and/or its nucleus by the cerebellar tonsils, ischemic damage of the eighth nerve/nucleus by the postero-inferior cerebellar artery and its branches, and inner ear fluid hypertension caused by the alteration of the CSF dynamic, which can also explain the vestibular pathway impairment with typical vertigo symptoms [38].

Most of the papers addressing this issue reported a high rate of audiovestibular symptom relief after neurosurgical posterior decompression [36, 38].

Oropharyngeal dysfunction (glossopharyngeal neuralgia)

Oropharyngeal dysfunction with CMI has not commonly described since the advent of easy availability of MR imaging, allowing a diagnosis even in very young children [3].

Indeed, the great majority of the children with CMI under 6 years of age (51% according to some series [3]) presents with oropharyngeal impairments, often associated with syringomyelia and scoliosis, rather than reporting the typical cough headache. Its incidence increases once the range of age is limited to the 0–2-year-old group (almost 78% of cases), when children rarely are able to describe pain and often present crying irritability and neck hypertension [53].

The occurrence of oropharyngeal involvement is related to the lower cranial nerve dysfunction, namely, the glossopharyngeal (IX) and the vagal (X) nerves, which appear as hiccups, cough, stridor, hoarseness of voice, gastroesophageal reflux, reduced gag reflex, vocal cord paralysis with dysphonia, recurrent aspiration and respiratory infections, palatal weakness, tongue atrophy, cricopharyngeal achalasia and dysphagia, poor weight gain, and failure to thrive [7, 12, 53].

These symptoms often precede or coincide with the onset of other lower cranial nerve dysfunction and respiratory problems, namely, sleep disordered breathing, and cardiovascular impairment; they rarely have been described as the only presenting symptom of CMI patients, mainly in the adult population [3].

The involvement of the IX and X cranial nerves may be explained by a mechanism compression/distortion of the brainstem induced by the tonsil herniation or by the presence of syringobulbia (SB).

In this regard, Menezes et al. [54] published interesting data on a series of 13 patients (aged 0–18 years old) who presented SB associated with CMI. They observed that CMI-associated SB usually has a chronic pattern, and it invariably results in cranial nerve dysfunction, with the prevalence of the IX and X cranial nerves, resulting in absent or reduced gag response (seen in 12 patients out the entire series). They also demonstrated the close relationship between syringomyelia (mostly cervical) and the occurrence of SB, postulating that the latter should arise due to upward extension of syringomyelia following the fiber tract. A dramatic improvement of the lower nerve palsies was depicted after posterior fossa decompression in both the series presented (studied in the same center), along with the resolution of SB on MR imaging [3, 54].

CMI-related glossopharyngeal neuralgia represents an extremely rare occurrence with only case reports addressing this issue [1, 46, 67]. Classically, it is caused by a neurovascular compression at the root entry zone of the IX cranial nerve, inducing demyelination and ephaptic transmission which leads to hyperactivity and hyperexcitability of the central neurons [46]. The supposed mechanism underlying the IX neuropathy in presence of CMI seems related mainly to the direct effect of the herniated tonsils on the nerve, pushing forward the posterior-inferior cerebellar artery [67]. Ruiz-Juretschke et al. [67] described a patient who underwent initially a standard posterior decompression of the occipitocervical junction, without tonsillar coagulation; however, the pain recurred after 3 months and subsided only after a second operation including the resection of the right cerebellar tonsil. On the contrary, other authors [46] recommend not to approach a glossopharyngeal neuralgia with CMI by means of a standard microvascular decompression procedure, since it may not be effective in the treatment of the other CMI symptoms.

Cardiovascular impairments

Cardiovascular manifestations have been seldom described in the literature, and once again, only case reports gave attention to their association with CMI [20, 29, 57, 63, 68, 71, 77]. The patients described are mainly young adults with a relatively long history of medical refractory cardiovascular disease; they had undergone extensive diagnostic workup which, ultimately, ended up into no control of the cardiologic symptoms. These may include syncope, sinus bradycardia, postural tachycardia (palpitations), and arterial hypertension, variably coexisting and/or associating with the typical CMI symptoms. Carcinogenic syncope may be mistaken with the rare occurrence of cerebellar fits, characterized by drop attacks with or without loss of consciousness, abnormal extensor posturing, and different degrees of respiratory impairment. These paroxysmal spells were seen more commonly in the pre-MRI era; the patients used to be initially studied for epilepsy and often had undergone evaluation with electroencephalography and/

or electrocardiogram and Holter monitoring before CMI diagnosis [60, 74].

Interestingly, most of the patients presenting cardiovascular disease with CMI gained a significant control or complete resolution of the cardiologic symptomatology after decompressive surgery, along with the other symptoms associated.

The generation of arrhythmia may be explained by the compression of the descending vagal fibers originating in the nucleus ambiguous, cardiovascular center of the medulla oblongata, and dorsal motor nucleus and ascending fibers from chemoreceptors, mechanoreceptors, and baroreceptors involved in cardiovascular autoregulation [20]. Differently, some hypotheses exist on the mechanism of hypertension in CMI patients: this may results as the effect of compression on the rostral ventrolateral medulla oblongata nucleus and the reticularis rostroventrolateralis nucleus which increase the peripheral vascular resistance, cardiac output, and secretion of catecholamines [29]. CSF flow alterations may be included in the physiopathogenetic process, since the observation of the possible role of disrupted paravascular/interstitial fluid exchange in the brain is seen in cases of normal pressure hydrocephalus (NPH) or non-communicating hydrocephalus. This had led to an increased age-adjusted prevalence of cardiovascular disease and diabetes in NPH [27]. However, according to a recent retrospective analysis, CMI patients presented a higher prevalence of diabetes (particularly in the male CMI population), rather than an increased incidence of arterial hypertension [27].

Sleep-related breathing disorders

Sleep-related breathing disorders (SRBDs) represent one of the sleep-related disorders listed in the International Classification of Sleep Disorders (ICSD-2) [24] and encompass a variety of abnormal respiratory patterns in sleep [44]. They are a chronic condition associated with disruption of sleep continuity and intermittent hypoxemia, leading to serious effects [25]. In CMI patients, the presence of SRBDs may be the cause for potentially fatal complications, namely, respiratory failure, post-operative susceptibility to respiratory failure, and sudden death [25, 44].

Several studies have been conducted on patients with CMI to assess the prevalence of SRBD occurrence, in order to define the actual relevance of the question on these patients' management. According to data from the literature, there is a wide range, accounting from 24 to 70% in the pediatric group [5, 21, 24, 51] and from 59 to 75% in the adults [25]. This great variability depends by the heterogeneity among the series of patients, most of the time with a low number of population each, different inclusion criteria, and scale of SRBD evaluation. Moreover, the cases included in the analysis, whether prospectively or retrospectively collected, were often referred from neurosurgical department, with a possible initial bias selection. Nevertheless, SRBD prevalence in both adult and pediatric CMI patients results higher than in general population [44].

The SRBDs are classified into three categories: the central sleep apnea syndrome (CSAS), the obstructive sleep apnea syndrome (OSAS), and the central alveolar hypoventilation syndrome (CAHS) [24]. CSAS and OSAS and mixed forms (MSA) are the most frequently described in association with CMI [24, 44, 51]. The former is characterized by a transitory absent or decreased effort to breathe, with 5 or more respiratory events lasting more than 10 s associated with microarousal and oxygen desaturation, depicted by the polysomnogram. OSAS are caused by a total or partial obstruction of the upper airway, with the same CSAS characteristics on polysomnogram [24].

In normal condition, automatic respiration relies on the activity of three interconnected groups of neurons, localized in the brainstem (Fig. 1): the pontine respiratory group, located in the rostral and dorsal pons; the ventral respiratory group, sited in the ventrolateral region of the medulla oblongata; and the dorsal respiratory group which is in the nucleus of the solitary tract. The first is involved in the central control of breathing (as a relay from suprapontine structures, amygdala and hypothalamus), with coordination of respiratory phase and integration of airway mechanoreceptor reflexes; the second is composed by the inspiratory and expiratory neurons which project to the intercostal and abdominal motor neurons. The last one represents the first central recipient of stimuli from mechanoreceptors, chemoreceptors, and baroreceptors [24]. In addition, lower cranial nerves (VII, IX, X, XI, XII) are responsible for innervating the upper airway muscles. This complex anatomical organization gives easily a reason to the appearance of breathing disorders in CMI. Indeed, suggested mechanism of CSAS origin includes a lack of functional chemoreceptor afferents for injury to the cranial nerve, insensitivity or overactivity of peripheral chemoreceptor due to brainstem involvement, compression of phrenic neurons in the cervical spinal cord because of a syrinx or compromised vascular supply to the brainstem, and anterior bulbar compression by an odontoid apophysis or posteriorly by the cerebellar tonsils [5]. On the other hand, OSAS is believed to result by a primary involvement of the IX and X cranial nerves, either by compression/stretching on the peripheral nerves or on their corresponding pontomedullary nuclei, leading to dysfunction of the pharyngeal and laryngeal muscles which induce a negative thoracic pressure and consequently inhalation to cause upper airway collapse (leu). Patients with CMI also can present anatomical anomalies that may contribute to the occurrence of obstructive events, namely, macroglossia, large neck size, and retrognatism [24].

Case reports and small series have depicted a high prevalence of central sleep apnea in CMI patients; on the contrary, a predominance of obstructive respiratory events is more commonly reported in series with greater number of patients [25].

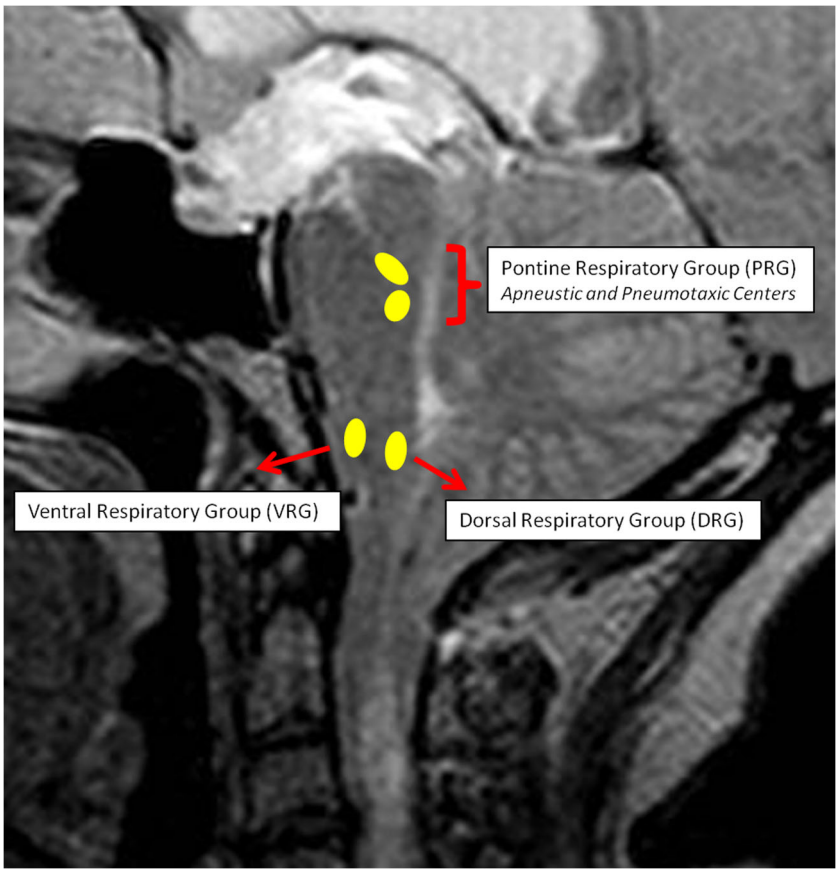

Fig. 1 Sagittal T2-weighted MRI showing a case of tonsillar herniation associated with hydrocephalus and cervical syringomyelia. Schematic localization of the main groups of neurons involved in respiratory control

Some reports in both adult and children CMI populations have described mixed forms on polysomnography, with an interesting tendency to change from one type of sleep apnea to another after treatment [44].

Clinical sleep history and physical examination are neither sufficient sensitive nor specific to establish a diagnosis of sleep apnea in CMI patients; therefore, polysomnography should be included routinely in the screening workup of CMI patients, including the asymptomatic group, to obtain correct information on the SRBD severity and characteristic in order to tailor the management decision [5, 25].

On a radiological point of view, the data from literature are discordant: the correlation between different findings and the severity of the SBRD in CMI remains controversial. Some authors [5] found that a greater degree of tonsillar herniation, with a cutoff ≥ 20 mm, was strongly associated with SBRD. Losurdo et al. [51] demonstrated that the presence of syringomyelia was associated with SBRD, but did not found any correlation with tonsillar ectopia. Hydrocephalus was found by the majority to play a decisive role in the occurrence of sleep apnea [25, 51]. Dhamija et al. [18] reported a significant difference between children with and without CSF effacement on neuroimaging, with the former having more frequently breathing disorders. CM type 1.5 has also been investigated on this issue. It represents a subgroup of CMI patients, whose cerebellar tonsils are seen in combination with brainstem herniation through the foramen magnum, resulting in downward displacement of the obex [25, 78]. However, recent studies failed to demonstrate a correlation between this condition and more serious SRBD manifestations [25].

Likewise, uncertainty derives from the outcome obtained after posterior fossa decompression. Most of the authors agree that significant improvement can be noticed in SRBD symptoms reducing the foramen magnum overcrowding [5, 24, 41, 44]; in particular, posterior fossa decompression proved to be effective in reducing mainly central respiratory abnormalities, rather than obstructive apnea, which may be related to other factors. Postoperative worsening of SBRD as well as recurrences has been also described [5, 44]. The correct management of these patients should therefore include posterior fossa decompression, continuous positive airway pressure, otorhinolaryngological surgery for peripheral obstructive causes, and positional therapy in cases presenting postural OSAS [24].

Epilepsy

As daily medical practice, the widening availability of MR imaging has increased the detection of Chiari I anomaly in a great number of patients who present for seizure occurrence. However,

literature lacks systemic analysis and specific data, with only a few papers addressing this issue [10, 11, 19, 34, 35, 40].

The proportion of epileptic patients among CMI is difficult to assess, with a range reported from 3.8 to 15% according to different series with variable inclusion criteria, not strictly comparable [34, 59, 73, 81].

The mean age at epilepsy onset in CMI varies significantly from the first year of age up to adulthood, with prevalence during late childhood [34]. It is generally characterized by a focal onset (with prevalent complex partial semiology), with rare secondary generalization. It has been described in association with mental retardation, speech delay, and autism, but more commonly as the first symptoms in otherwise asymptomatic CMI patients, as in febrile convulsion episodes [9, 34]. The frequency of epilepsy may be worsen by the occurrence of SRBD [51].

The antiepileptic drugs result easily effective in controlling seizure, whereas surgery on posterior fossa did not prove to influence directly the epileptic outcome, with exception in the cases described by Buoni et al. [11] who reported the disappearance of focal intermittent rhythmic delta activity after foramen magnum decompression.

The origin of epilepsy in these cases has been explained by several theories, including the coexistence of hidden microdysgenesis over the cerebral cortical surface or a direct involvement of cerebellum in the control circuitry of cortical hyper-excitability [19, 34].

The former has being pointed out in several studies focusing the attention on the particular association with cognitive impairments in CMI patients, resembling a specific syndrome, with the aid of functional radiological studies, which will be discussed extensively in the next paragraph [35, 40, 42]. On the contrary, a specific role of the cerebellum in the epileptogenesis has not yet been demonstrated; the absence of a radiological correlation between the degree of tonsil herniation and the effectiveness of medication on seizure control, independently on whether the patients were operated or not, does not support a straight relationship [34, 35]. Lastly, it may be the expression of simple casualty with no direct intercausality relationship, this being an association between two frequent disorders [34].

As far as we know, there may exist different subcategories of CMI patients presenting epilepsy, because of different pathogenetic backgrounds [34].

Cognitive impairment

Cognition impairment in CMI patients has been increasingly depicted in daily practice and reported in the literature since the last decade, providing the starting point for the wide spreading of investigational studies [39]. Indeed, over 40% of CMI patients report subjective cognitive symptoms, experiencing “brain fog” and disruption in concentration [26, 39].

According to the extensive literature review by Rogers et al. published in 2018 [66], the actual overall scientific production presents a low quality of evidence because of several methodological biases among each paper, namely, small sample size, study populations often unrepresentative of broader CMI population, heterogeneity of selection and detection measures, or routinely ignoring any relationship with specific CMI-related signs or symptoms.

With the limit of the aforementioned possible misleading factors, most of the studies pointed out that CMI patients do not generally present deficit in general cognition, processing speed, learning, and memory, but showed more frequently impairments in executive function, attention and working memory, visuospatial, and perceptual skills [66]. Language development resulted mainly compromised in pediatric rather than in adult populations [66]. All these elements, taken together, resemble the cerebellar cognitive affective syndrome or Schmahmann’s syndrome [8, 39, 66].

One of the main criticisms on the results of the studies performed so far is the difficulty in identifying purely cognitive deficits, abstracting them from the countless associated CMI clinical conditions. The presence of epilepsy, with or without clear supratentorial microdysgenesis, may decrease the cognition profile [34]. The occurrence of SRBD may determine daytime drowsiness due to an increase in sleep fragmentation, REM parasomnias, and insomnia, inevitably influencing the cognitive performances [24]. CMI patients report often headache and chronic pain that may affect most cognitive functions, exacerbating known deficits or provoking cognitive vulnerabilities, but also modulates the processing of information with an emotional context [39, 66].

Allen et al. [4] studied the cognitive profile of a series of CMI patients who had already undergone decompression surgery using control methods to distinguish between measures of anxiety and depression (likely related to chronic pain) and cognitive symptoms. They further aimed at reducing the risk of patients’ anxiety for the imminent surgery. They provided evidence that CM patients show deficit in response inhibition, working memory speed, processing speed, and deficits in episodic recall. In particular, working memory, processing speed, and episodic memory appeared significantly compromised than did in controls, but group differences were eliminated when statistically controlled for chronic pain and anxiety and depression effects. On the contrary, in this study, response inhibition deficits persisted in the CMI patients even after statistical control for anxiety and depression effects. This observation raised the question on whether the cerebellar and/or brainstem damage in CMI may somehow influence the inhibitory control processing circuit (the fronto-parietal pathway) localized on the dorsolateral prefrontal cortex, the anterior cingulate cortex, and the parietal areas; however, neuroimaging studies are still claimed to validate this interesting hypothesis (Fig. 2).

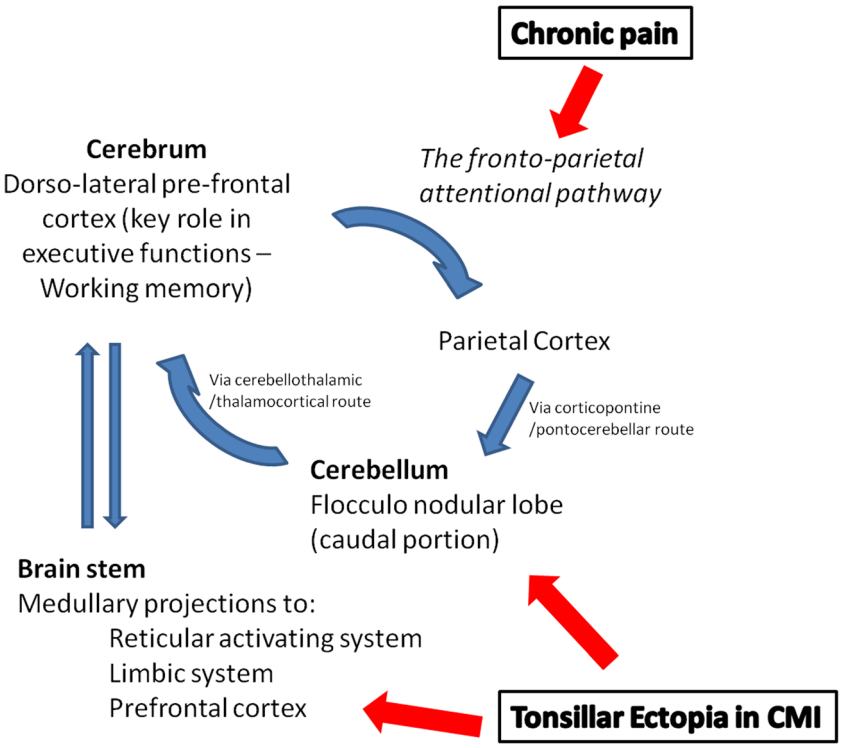

Fig. 2 Schematic summary of the fronto-parieto-cerebellar circuitry supposed to be involved in cognitive impairment associated with CMI

Houston et al. [39] examined cognitive and emotional processing deficits associated with CMI using a dual-task paradigm, along with recording event-related potentials (ERPs), arguing that CMI is both indirectly associated with cognitive decline due to comorbid anxiety and depression (as consequence of chronic pain) and directly associated with decline due to CMI pathophysiological processes. They observed that CMI patients did not experience deficits in cognitive control, but response times and emotion regulation appeared to be affected. Moreover, while single-task response time was no longer a predictor of CMI status after controlling for chronic pain and related factors, dual-task response time remained a significant predictor of CMI status, suggesting that the CMI-related deficits at least partially stem from CMI pathophysiology rather than chronic pain and related factors. In particular, P1 ERP (marker for integrative visual processing from secondary visual areas) and P3 ERP waveforms (known to measure effortful and motivational—conscious—cognitive processes) were maintained, and a frontalization of ERP amplitude was detected as a possible compensatory recruitment. Divided attention (the ability to attend to multiple stimuli and do various tasks at a time) was not apparently affected in CMI patients.

Beyond the traditional investigations on anterior cerebellum role in coordinating movement, the interest of the cerebellum involvement in neurocognitive processes has been emerging during the last two decades, noting mood fluctuations, dementia-like conditions, psychosis, and limited cognitive functioning in cerebellar diseases and lesions [39, 66].

The anatomical rationale for cognitive involvement in CMI disease is based on the assumption that several portions of the posterior cerebellar regions have known connections with the prefrontal cortex, namely, the flocculonodular lobe [4]. Likewise, a possible mechanism of interference on prefrontal cortex executive function is compression on the medulla, where the fiber tract damage may alter functions of the medullary projections to the reticular activating system, the limbic system, and the prefrontal cortex [4].

Kumar et al. [42] published in 2011 one of the most cited studies performed to assess a correlation between the appearance of radiological anomalies in the cerebrum and the occurrence of documented neuropsychological deficits in CMI patients. Using conventional MRI with diffusion tensor imaging (DTI), they were able to depict significantly decreased fractional anisotropy (FA) along with increased mean diffusivity (MD) in genu, splenium, fornix, and putamen (possible expression of elimination of dendrite arborization); and increased axial diffusivity in putamen, thalamus, and fornix, whereas radial diffusivity significantly increased in fornix and cingulus (probably for abnormal myelin integrity). All these elements correlated with abnormal neuropsychological test scores. Abnormal changes in the magnitude and anisotropy of water diffusion using DTI in patients with CM-I may therefore indicate microstructural abnormalities in the different brain regions/tracts, even when they appear normal on conventional MRI and may form the basis for neurocognitive deficits in these patients. Likewise, significant differences in axial diffusivity at the level of the middle cerebellar peduncle

were detected in symptomatic versus asymptomatic CMI children [22].

Another intriguing issue concerns the influence of surgery on cognitive performance. Actually, there are only a few reports addressing this argument, with debatable results [28]. According to the authors, CMI patients, both surgically treated and those who have not been decompressed, had a lower cognitive performance compared with healthy controls, even after statistically controlling for the influence of perceived pain and anxious-depressive symptomatology. They demonstrated a similar cognitive profile between both groups, suggesting that having undergone decompression surgery does not modify the cognitive performance. However, these results are burdened by the limit of comparing two different populations of patients, with no data concerning the cognitive profile of patients studied pre- and post-operatively.

Behavioral disorders

Neuropsychiatric disorders have been increasingly reported in the literature, although they are randomly depicted. Anxiety and depression are commonly seen in CMI patients with chronic pain [4]. However, an altered pain perception in CMI has been described as well, mainly related to mood disorders [17]. The aforementioned cerebellar cognitive affective syndrome can itself include an affective component, which may manifest as panic and anxiety, dysphoria and depression, irritability and aggression, or ruminative and obsessive behaviors; they have been described in previous cases and cohort reports on CMI patients [66].

CMI patients also experience difficulty in processing emotional content as originating from conscious, controlled processes [39].

There is no sufficient evidence that affective disturbances in CMI patients are related to the organic neuropathology, inducing an imbalance of brainstem structures controlling anxiety; these are mainly localized in the locus coeruleus, which is the major source of noradrenergic input to the cortex or the serotonergic dorsal and medial raphe nuclei [13, 53, 66]. The alternative explanation may simply account for the understandable reactions to chronic psychosocial stressors including the CMI condition and associated disabilities, in susceptible patients [71]. Moreover, there is no evidence of surgical influence on behavioral manifestations.

Conclusions

As a matter of fact, the comprehension of Chiari malformation type I has been evolving since the first description in 1891, including a wider range of clinical manifestations. There is no clear explanation on why some patients may exhibit uncommon symptoms, often in association with the most frequent ones, but even reported as single initial clinical occurrence. Their actual incidence may have been roughly underestimated in the literature so far, because of variable attention and sensibility in depicting them and correlating their onset with the malformation by different examiners, often not specialized in all medical fields. Moreover, the heterogeneity of selection and analysis among different studies prevents any univocal interpretation.

Interestingly, most of the authors appear sharing the impression that surgical decompression plays a significant role in controlling the majority of these symptoms, stressing the importance of their occurrence in relation with the malformation, thus widening the surgical indication. However, there are no yet comparable results concerning which kind of surgical approach should be proposed.

A routinely multidisciplinary clinical approach is becoming, therefore, advisable to encompass the diversity of conditions potentially associated with CMI and improve the care of CMI patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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