Towards a unified theory of Chiari Malformations

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TOWARDS A UNIFIED THEORY OF CHIARI MALFORMATIONS

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TABLE OF CONTENTS

1- SUMMARY

More than a century has elapsed since the first case of ectopia of the cerebellar tonsils through the foramen magnum was described by Hans Chiari (1891) and became known as Chiari Malformation. In the following decades a considerable bulk of clinical research was published on similar conditions along with its variants, giving rise to an entire spectrum of Chiari Malformations with changing definitions over time.

Further research in the last decades has then focused on more pre-clinical data, such as the embryology of the posterior fossa and its genetics determinants, or the mathematical modelling of cerebrospinal fluid (CSF) dynamic across the foramen magnum as well as the best radiological assessment for such a condition. Even more recent works mainly from western countries have used large population-based data as well as pooled analysis on multiple epidemiological studies to look at sociodemographic determinants of Chiari malformations.

It is now clear that the simple ectopia of the cerebellar tonsils and its variants reflect different conditions with different explanations and mechanisms so that some authors have provocatively suggested that Chiari Malformation does not exist as such, and that when facing an ectopia of the cerebellar tonsils we should look at any possible explanation leading to such a condition, and only then look for the right treatment.

Following a "reductionist approach", that is to say looking at small simple elements of a complex problem, current concepts about the ectopia of cerebellar tonsils can be reduced to three main explanations: posterior fossa disproportion (from mesodermal origin), CSF impairment between cranial and spinal compartments and craniovertebral junction instability.

This framework can account for the heterogenous clinical scenarios observed (from completely asymptomatic to multiple neurological and spinal complaints) as well as for various radiological findings encountered not only in the posterior fossa but also in the cranial compartment (e.g. ventricular abnormalities, dural venous changes, cranial vault malformations, etc.) and in the spinal compartment (e.g. craniovertebral junction abnormalities, thoracolumbar deformities, syringomyelia, tethered cord and dysraphisms, etc.). Finally, this heterogeneous model can account for different surgical options and why sometimes they fail and sometimes succeed.

If we do accept the challenge that Chiari Malformation as such does not exist, we can state that such a framework can constitute a unified practical theory to explain the ectopia of cerebellar tonsils: the choice of the nomenclature then becomes a pure semantic matter.

2- INTRODUCTION

There is only one single common feature in the realm of what is called "Chiari malformations": they all involve the posterior fossa and, variably, its content. In particular, the definition of Chiari I malformation (CM-I) continues to evolve.

Since its first description in 1891, and despite a considerable amount of literature published over more than a century, there is little consensus about its origins, its pathophysiology, and its best treatment, making it an interesting topic for neurosurgeons.

The clinical scenario offered by Chiari malformations vary, from completely asymptomatic to severe brainstem and/or spinal cord symptoms, and a multitude of neurological focal deficits.

The effort done by researchers over time has led to many definitions, with now at least 4 types of Chiari malformations and a few subtypes. Its pathophysiology variably involves a malformative background, neural compression mechanisms, cerebrospinal fluid (CSF)/intracranial pressure (ICP) impairment, spinal changes and craniovertebral junction (CVJ) abnormalities. Its treatment can span from abstention to simple bony decompression of the foramen magnum, to more complex procedures involving neural elements decompression, CSF diversion and spinal instrumentation.

This work is intended to summarize the different pathophysiological aspects that Chiari malformations can display, if such malformations can ever exist under a unique name; we will then summarize the theories behind their current clinical management, with a special interest on the CM-I, the most represented one. We will focus more on the role of CSF impairment in its pathogenesis, particularly for syringomyelia, hydrocephalus and idiopathic intracranial hypertension and hypotension.

We will briefly overview the nomenclature and the embryology relevant for the Chiari malformations as well as its bibliometric and epidemiology, before focusing on aspects relevant to the clinician.

We will then discuss what is named "Complex Chiari malformation"(CCM), which variably involves ventral brainstem compression and CVJ instability. Finally, by highlighting its heterogenous nature, a final discussion will provide a practical unified theory to help the clinician dealing with low-lying tonsils.

2.1 Nomenclatures of Chiari malformations

The first description of the Chiari malformation dates back to 1891: Hans Chiari reported on a 17 year-old girl with a "cone shaped projection" of the cerebellar tonsils into the cervical spinal

canal [1]. Subsequently, he described three types of the same malformation with some further amendments based on which content of the posterior fossa was displaced into the spinal canal[2]. By the end of the 19th century this gave rise to many evolving definitions (and disagreements) about the nomenclature, with some variants (e.g. Chiari 3, Chiari 3.5, Chiari 4) described only in small series or even only in single case-reports [3].

In 1894 Julius Arnold reported on a patient with herniated fourth ventricle and cerebellum [4] (a pattern similar to what is termed now termed Chiari 2). Chiari himself described a similar case the following year[2]. Subsequently, two of Arnold's students introduced the term "Arnold-Chiari malformation" [4] but the eponym Chiari 2 remained preferred by many. For this reason, the term Arnold-Chiari malformation should correspond only to the Chiari 2 malformation.

Chiari 1

It is defined as the ectopia of the cerebellar tonsils by more than 5 mm below the McRae's line (basion to opisthion) [3]. The value of 5 mm was first introduced in 1985, in a MRI-based study assessing the positions of cerebellar tonsils in both normal asymptomatic population and in patients with symptoms. The 5 mm cut-off was found to have a sensitivity of 92% and a specificity of 100% in further studies with a small sample [5] and has remained widely agreed upon. Much larger series of several thousand patients found subsequently that ectopia of more than 5 mm can be found also as an incidental finding in asymptomatic patients, ranging from 0.7% to 3.6%. Similarly, the incidence of CM-1 related syringomyelia is reported with an incidence varying from 12% to 65%, depending on the studies and their relative selection biases [6]. Table 1 summarizes the current nomenclature and features of the Chiari malformations.

Chiari 0

The presence of syringomyelia without tonsillar ectopia *that resolved after* foramen magnum decompression was reported in 1998 [7] and it was confirmed by other studies. This condition became known as Chiari 0. Structural abnormalities in the posterior fossa and its content altering the CSF flow at the foramen magnum have been proposed as possible pathophysiological mechanisms (i.e. obex below the foramen magnum and descent of the brainstem, enlarged antero-posterior brainstem diameter, increased basion-opisthion distance, shorter clivus with increased tentorial angle)[8].

Chiari 0 malformation can be defined only *postoperatively* (by the resolution of the syringomyelia after the foramen magnum decompression), and is therefore not distinguishable

before surgery from a true idiopathic syringomyelia, provided that other abnormalities (such as tethered cord, tumours, trauma, arachnoiditis) have been ruled out.

Chiari 0.5

It has been recently introduced and defined as an ectopia of cerebellar tonsils anterior to the spinal cord [9]. In this subset of the Chiari malformation, patients seem to have more often dysphagia, sleep apnoea and behavioural problems compared to classic CM-1, regardless of the amount of displacement of the tonsils [9]. Under this definition, CM-0.5 can be seen as a variant of CM-1 or CM-0.

Chiari 1.5

Firstly described in 2004, it entails an ectopia of cerebellar tonsils of more than 5 mm with a caudal displacement of the brain stem [10], thus reminding the CM-2 malformation, but without spinal dysraphism, herniation of the vermis or large massa intermedia and other supratentorial abnormalities[11]. It becomes then difficult to distinguish clinically CM-1 from CM-1.5 patients, since presenting symptoms appear to be similar, and many studies do not differentiate these two entities, making its real incidence more elusive. This pattern of the malformation seems to be more prone to a higher risk of cranio-vertebral junction instability requiring fusion [12].

Chiari 2

It was first described by Arnold [13] as a displacement of the fourth ventricle and vermis and brainstem into the cervical canal. It is a different entity from the CM-1 (and its variants). It is invariably associated to patients with myelomeningocele and many patients show low insertion of the tentorium to the occipital bone, tectal beaking, large massa intermedia and enlarged foramen magnum [14]. Patients present more often with lower brainstem dysfunction, stridor and hypotonia [15]. There is wide agreement on its pathogenesis being related to in utero leakage of CSF, impeding dilatation of the primitive ventricles and causing hindbrain herniation. This is also supported by the lower incidence of the malformation in foetuses undergoing in utero repair of myelomeningocele [16].

Chiari 3 and Chiari 3.5

There are only around 60 cases reported in the literature describing an herniation of posterior fossa contents through a occipito-cervical defect, creating an encephalocele[17] and referred as CM-3. A variant of this malformation is named CM-3.5 and it has been described only once: it

consisted of extensive congenital anomalies of the cervical spine and its content as well as fistulous tract between posterior fossa and oesophagus[18].

Chiari 4

Historically it was first described by Hans Chiari himself as an occipital encephalocele with herniation of both occipital lobes, cerebellar hypoplasia and absence of tentorium. Nowadays the term is used mainly for cerebellar hypoplasia[3].

Table 1: current nomenclature of Chiari malformations and their specific features:

Malformation and subtypes	Definition	Features and origins
CM 1	Ectopia of cerebellar tonsils by 5mm or more below McRae's Line	
CM0	Syringomyelia without other causes that responds to posterior fossa decompression. No tonsillar ectopia	secondary manifestation of one single genetic/developmental problem (in which case CM1, 0, 0.5, 1.5 are a continuum) or
CM 0.5	Ventrolateral herniation of cerebellar tonsils (anterior to a line passing through the middle of the medulla at the foramen magnum	CM1 is a secondary manifestation of multifactorial abnormalities, both congenital or acquired (in which case the eponym is a misnomer)
CM 1.5	Ectopia of cerebellar tonsils and of the brainstem (obex below McRae's line) by more than 5mm	
CM 2	Ectopia of cerebellar vermis and brainstem into the cervical canal, associated to a myelomeningocele	Hindbrain distortion from an open neural tube defect
CM 3	Ectopia of cerebellum and brainstem into a defect of the craniovertebral junction with encephalocele	

CM 4	Cerebellar hypoplasia with occipital encephalocele	Genetic/teratogenic/developmental disease

2.2 Embryology of the posterior fossa relevant to the Chiari malformations

We will briefly review the more salient elements in the development of the posterior fossa and refer the reader to classic embryology textbooks for the definitions of structures mentioned below.

The sclerotogenesis (the development of transient embryonal tissue from somites deriving from the mesoderm) and the development of the vertebrae start at the end of the 4th week of gestation.

It is important to note that the development of the craniovertebral junction differs from the development of the vertebrae below C2. We kindly invite the reader to refer to the works of Shoja et al. [19,20]

Relevant points to the Chiari malformations from embryological studies can be summarized as follows[21]:

- Hindbrain herniations is associated with proatlas segmentation malformation in 33% of cases.
- Atlantooccipital assimilation is the most frequent anomaly found in Chiari malformations, suggesting that abnormalities of the atlas are common in hindbrain herniation and this can be related to an underlying ontogenetic error.
- Basicranial angle (angle formed between the lines nasion-dorsum sellae/dorsum sellae-basion) is greater in patients with CM-I.
- Basilar invagination (when the most caudal part of the occipital bone is displaced upward and inward and the vertebral column and the skull approximate each other) can be divided into two groups: with or without CM-I.
- Patients with CM-I malformation have shallow posterior fossa, thus reflecting an abnormality of the occipital squamous bone limited to its cartilage-derived part. Namely, supraoccipital, exoccipital and basioccipital parts of the occipital bone are underdeveloped to a various degrees in such patients.
- Chamberlain's line (line going from the posterior tip of the hard palate to the opisthion) is shorter in patients with Chiari I malformation, suggesting an anomaly of the midface.

- Cerebellum in patients with CM-II malformation is smaller, secondary to hypoplasia or atrophy which affect mostly the lateral hemispheres, whereas elongation of the vermis probably results from lateral compression in a rigid posterior fossa.
- Tentorium is often dysplastic, and its attachment low towards the foramen magnum in patients with CM-II malformation.
- In CM-I malformation the tentorial region expands upwardly to compensate the overcrowding posterior fossa.

Many pathophysiological theories have been proposed in order to explain hindbrain herniation, hydrocephalus, syringomyelia and various other brain and craniofacial abnormalities found in Chiari malformations. Some of these theories overlaps (stressing on one mechanism over the another), or are opposing views on what primary event is causative for the other (e.g. if hydrocephalus is causing hindbrain herniation or vice-versa).
Overall, if we were to take these theories together, we will find the following (rather confusing) list :

- Hydrocephalus and pressure coning theory
- External compression theory
- Posterior cranial fossa overcrowding theory
- Hydrodynamic theory
- Occipital dysplasia theory
- Neural tube overgrowth / disorganized neural tube growth theory
- Neuroschisis theory
- Cord traction (or tethered cord) theory
- Developemental arrest theory
- Inadequate ventricular distension theory
- Craniocervical growth collision (or caudocranial reversed vertebral growth) theory
- “Suck and slosh” theory
- Exaggerated spinal CSF systolic wave theory (especially for syringomyelia)

None of these theories proved irrefutable and superior to the others, and each accounts for some findings in specific patterns of the malformations.

We can reasonably state that whichever the *primum movens*, some disturbance in CSF dynamic between the cranial compartment and the spinal compartment must come into play and give rise to the Chiari malformations pattern.

2.3 Bibliometrics on Chiari malformations

At a broad view, when enquiring Pubmed about Chiari malformations the results vary according on the keys that are entered:

As of April 2024 the following numbers can be retrieved:

- 13'204 results for "Chiari"
- 5'761 results for "Chiari malformation"
- 4'810 results for "Chiari malformations"
- 4'699 results for "Chiari I malformation"
- 4'428 results for "Arnold Chiari malformation"

A more accurate analysis, which applied specific selection criteria, has been done as of August 2022; this provides with a bibliometric study on the 100 most cited article on the topic[22], arguably the best available knowledge on the topic for the clinician.

When looking at the timeline of the most cited articles, the majority of the work has been produced between the '90s and the 2010s.

The work of Milhorat et al. [23] is the top one (896 citations) and is also the most cited-per-year article on the topic. Most cited articles are respectively from the United States, United Kingdom, Italy, Spain, Japan, Germany, Canada, Colombia, Norway, Argentina, Turkey, India, Brazil and France [22].

Most of the articles (n=69) were observational studies (retrospective and prospective), 16 were descriptive studies and 15 reviews (including 2 systematic reviews). Of note, no randomized studies have been found among the 100 most cited articles [22].

Understandably, most of the studies relate to CM-I, followed by CM-II, and a minority on both. Around 40% of the most cited articles relate to paediatric population, another 30% mixed paediatric and adult population and another 30% adults only [22].

The topics that were most covered among the 100 studies were imaging, followed by outcome of surgical treatment, clinical signs and symptoms, surgery, diagnosis and pathophysiology [22].

We can infer that most of the clinical practice based on the Chiari malformations derives from observational studies on CM-I and on paediatric population, and mainly focused on imaging findings.

A definition of practical usage (a "working definition", so to speak) for Chiari malformations, that is not uniquely based on radiological findings, can be derived by the most cited articles on the topic [22,23]. Here the CM-I becomes a disorder of mesodermal origin based on 4 main findings:

- No evidence of neuroectodermal defect
- Appearance of secondary effects of chronic tonsillar herniation
- Similar incidence among close relatives
- Associated anomalies of the posterior fossa and craniovertebral junction

After decades of competition between theories to explain its pathophysiology (on one side theories based on structural developmental disorders and on the other theories based on hydrodynamic disorders) , a disruption occurred: in 2015 Atul Goel et al. published a study on 65 patients with CM-I who were treated by atlanto-axial fixation. It offered a completely new paradigm for the CM-I, suggesting atlanto-axial instability as its *primum movens* and consequently the tonsillar ectopia as a "nature's protective air bag" to mitigate brainstem compression from the instability. This led to the claim that posterior fossa decompression could be even detrimental in the long term, since it does not address the main pathological mechanism [24]. From its publication in 2015, Goel's article quickly ranked 29th article among the 100 most cited ones [22].

2.4 Epidemiology and genetics of Chiari I malformation

Incidental cerebellar tonsils ectopia is increasingly reported on MRI while its clinical significance is uncertain : it becomes then important to differentiate the radiological prevalence from the clinical prevalence, the symptomatic cases from the asymptomatic cases.

Based on healthy adult volunteers (over 45 yo), 0.9% of a cohort of 2000 individuals had incidental lower displacement of cerebellar tonsils fitting the definition of CM-I [25]. This prevalence is probably underestimated since it excluded paediatric and symptomatic population.

Many studies found that actual tonsillar position in the general population follows a normal distribution and the 5 mm cut-off for the displacement of the herniation is at the lower end of this distribution, regardless of the clinical consequences for a given individual [26]. If this holds true, then patients suffering from CM-I symptoms are outliers along this normally distributed tonsil position.

Imaging studies suggest the that prevalence is between 0.24 and 3.6% and of these, only 32 to 63% are symptomatic[6,25]. Prevalence of symptomatic tonsillar herniation seems to be around 7/100'000 in two different large cohorts from the US and Europe [6,27]. However, multiple factors

must come into play when reporting the prevalence of symptomatic and asymptomatic herniation, including age, sex, ethnicity and socioeconomic status. The same challenge of reporting its true prevalence is encountered for syringomyelia associated with CM-I, since patients with neurological symptoms are more likely to undergo imaging and have a syrinx diagnosed [6,28], even more so in surgical series. In the large radiological study from Strahle et al. done on 14'116 children, 23% of the patients harbouring a CM-I had an associated syrinx, which account for around the 0.83% of the whole population[28]. In a large northern Italian cohort, the prevalence of a symptomatic syrinx was 4.8/100'000 [27]. Generally speaking, it seems that patients with lower tonsillar position tend to develop syrinx more frequently [28]. Age seems also related to CM-I and syrinx prevalence, where it has been measured at 0.97 to 3.6% in the paediatric population [6,28], and lower (0.9%) in only adult population [25]. This could be explained by an age-related rostral change in the position of the cerebellar tonsils , where the nadir seems to be reached at age between 21 to 30. Same applies to the rate of detection of syringomyelia, which seems to be higher in the first 5 years of life. Consequently, younger age seems to be related to the presence of symptoms at the time of CM-I diagnosis [28].

A female predominance has been reported, with a F:M ratio varying from 1.3:1 to 4:1 [28], while ethnic, racial, and socioeconomic determinants are somewhat a new area of study. As an example, in a nationwide survey in Japan, the prevalence of syringomyelia associated with CM-I was 0.93/100'000 , much lower than the one reported in the northern Italian cohort[27]. On the other end, in a specific region of the Republic of Tatarstan (Baltasy district) patients have a 10-fold likelihood of being diagnosed with CM-I compared to the rest of the national population, probably because of family clustering. In the US, African-American patients were found to harbour lower tonsillar descent and syringomyelia as well as presenting with symptoms at diagnosis and age at diagnosis was older in patients with public insurance coverage, regardless of their ethnicity [29].

Overall, natural history of CM-I and syringomyelia is benign for most patients, with fairly stable position of tonsils over time as well as light symptoms (when present). On large cohorts of patients with CM-I - with or without syringomyelia - and managed conservatively, only 3,5 to 16% required surgery [30]. So far, no studies has randomized patients to surgical interventions and - since conservative management is not prescribed on randomized basis - patients undergoing conservative management are likely to be less symptomatic than those with more progressive symptoms.

Little is known about genetic of CM: most of genetic conditions that display also CM-I (e.g. Klippel Feil syndrome, achondroplasia, Hadju-Cheney syndrome, Ehlers-Danlos syndrome) involve cartilage and bone disorders. Besides a considerable number of case reports on CM-I and heritable connective tissue disorders, a significant contribution to the possible mechanisms leading to cerebellar tonsils herniation came from Milhorat et al. in 2010: he studied the posterior cranial fossa volume and the size of the occipital enchondrium in 741 patients with CM-I, and paired them with with 80 matched-controls. Although only 388 patients showed reduced size and volume of the posterior fossa, the remnant showed normal values but had concomitant findings, such as: 225 individuals harboured occipitoatlantoaxial instability, 55 tethered cord syndrome, 30 intracranial masses and 28 had lumboperitoneal shunts. This led to a proposal of 5 possible mechanisms accounting for CM-I: cranial settling, cranial constriction, cord tethering, occipitoatlantoaxial instability, CSF hypotension[31]. However, most of patients harbouring CM-I will present it as an isolated condition (non-syndromic). The most recent and robust study on the genetic basis of isolated CM-I is from 2021 and showed a high prevalence of genetic variants in chromodomain genes (CHD3 and CHD8), with most of the mutations being *de novo.* These genes have a regulatory function on the expression of many other genes involved in neurodevelopment, as well as the extracellular matrix and the skull, suggesting a multigenic malformation of one or more systems (CSF, vasculature, bone, brain).

3- DIAGNOSTICS OF CHIARI I MALFORMATION

3.1 Clinical manifestations of Chiari I malformation

The clinical manifestations of CM-I vary depending on the extent of the disruption of CSF dynamics and the impaction of the cerebellar tonsils on the foramen magnum contents.

Bearing in mind that 15% to 37% of patients with tonsillar ectopia on imaging are considered asymptomatic[6], here we summarize all possible clinical manifestations linked to the CM-I based on an symptoms-related approach and on an age-related approach:

- *Headaches*

They have a variably reported prevalence in Chiari patients but no specific criteria exist to diagnose a *Chiari headache.* Classically, headaches have been described as occipital/suboccipital, magnified by Valsalva manoeuvres, lasting less than 5 minutes, frequent and intense. Sneezing, coughing, laughing, screaming, defecating, jumping and any activity that prompts a Valsalva manoeuvre can elicit headaches and most patients tend to show more symptoms rather than only headaches.

- *Scoliosis (levoscoliosis) and syringomyelia*

These are the most common concurrent diagnosis associated with CM-I. Namely, syringomyelia can be located at the cervical cord, at the cervicothoracic cord, thoracic cord and lumbar cord as well as the whole spinal cord (holosyrinx). When symptomatic, usually patients show upper extremity weakness (hand), pain and sensory loss in a "cape-like" distribution (from anterolateral spino-thalamic tract involvement) with preservation of epicritic and proprioceptive sensory function (subserved by the dorsal columns system). Absence of abdominal reflexes ipsilateral to the convexity of the scoliosis can be found.

Scoliosis has been found in 31% of children with syringomyelia and, as a general rule, most patients with CM-I and scoliosis have also syringomyelia, but not all patients with CM-I and syringomyelia have scoliosis.

- *Signs from compression at the cervicomedullary junction*

These are much less frequent and may involve compression of medulla (affecting respiratory pattern and sleep apnea), brainstem and cervical cord (with sensorimotor deficits or even spasticity) , lower cranial nerves (tipically in children younger than 3, causing dysphagia, dysarthria, dysphonia, abnormal extraocular motility), cerebellar flocculus (causing gaze-evoked nystagmus), outlets of the 4th ventricle (leading to hydrocephalus). A particular subset of symptoms, related to the compression at the medulla/lower cranial nerves, goes under the name of Sleep-Disordered Breathing (SDB). This usually refers to apneas and or hypopneas during sleep, leading to hypoxia and sleep disruption overnight and further sleepiness during the day. SDB is either central (where the inspiratory input doesn't occur) or obstructive (from pharyngeal collapse) and are more frequent in CM-II than CM-I. A recent cohort of 465 patients with CM-I showed that 44% had SDB but this may not be representative of its true incidence since not all centres perform sleep studies on such patients.

- *Orthostatic intolerance*

This term usually refers to unspecific symptoms like fatigue, light-headedness, syncope, all provoked by the upright posture and improved by recumbency. Orthostatic intolerance within CM is possibly related to either CSF flow disruption or to dysregulation of the major cardiocirculatory centres of the lower brain stem. Indeed orthostatic intolerance (OT) can be found as well in a number of other conditions altering the neuroanatomy of the skull base, cervical spine or craniovertebral junction. Similarly, conditions harbouring connective tissue laxity can also present with OT. There is not clear pathophysiological description of CM-I and OT but a growing number of case reports has shown improvement of OT symptoms after posterior fossa decompression. Most likely, OT reflects a dysregulation of the normal neural

response to the gravitational pooling of blood (500 to 1000 ml) while adopting an upright position and consequent lowering of cerebral blood flow.

Another approach to the clinical manifestations of CM-I is based on the age-group rather than the anatomical structures involved. This can be helpful especially in the paediatric practice, considering the inability of very young patients to communicate and the changing morphology of these patients.

- *Neonatal period and infancy (0-3 years)*:

Clinical presentations is mostly related to pain and compression at the cervicomedullary junction. Pain is usually derived from irritability, cries, night-time waking, opisthotonos, neck extension and arching, behavioural patterns reaching for the head or neck. In this age-group one of the most common symptom is oropharyngeal dysfunction, related to brainstem or lower cranial nerves involvement. This can lead to dysphagia, choking, poor feeding and failure to thrive, gastroesophageal reflux, cough, snoring and stridor. These symptoms are even more exacerbated and frequently encountered when there is associated ventral compression of the brainstem from craniovertebral junction abnormalities (e.g. basilar invagination or dens retroflexion).

- *Toddlers (3-5 years)*:

Children in this group of age can verbalize their discomfort at the occipito-cervical area, relatable to headaches and frequently present already scoliosis and/or syringomyelia

- *Childhood and adolescence (5 years and older)*:

Patients in this age-group tend to be more reliable and report classic symptoms of CM-I as described above, particularly from cranial nerves involvement. It is important to note that scoliosis and syringomyelia in CM-I can lead to myelopathic syndromes even in absence of headaches.

- *Adults*:

  Symptoms in order of frequency include headaches, sensory changes, gait disturbances and less frequently oropharyngeal and cranial nerve problems. Of note, very rare acute presentations of CM-I have been reported, including dysphagia, isolated sensorimotor deficits, respiratory distress, gait problems, foot drop, anisocoria. Acute onset of symptoms of CM-I is very rare and usually it has inciting event (e.g. trauma, infection) and respond well to surgical decompression.

3.2 Imaging for Chiari I malformation

CM-I is classically defined by an inferior ectopia of cerebellar tonsils of 5mm or more below the McRae's line (from basion to opisthion, which defines the plane of the foramen magnum). As previously stated, this 5mm threshold is somewhat arbitrary and does not always correlate with symptoms that can be present even with a less or no tonsillar descent [23].

We must stress again that diagnosis of CM-I based on such a definition has rapidly increased in number over the last decades [6] and its prevalence is estimated to be around 0.77-1% [6] whereas syringomyelia - defined by some as a dilation of the central canal of more than 3mm - has a prevalence varying greatly between 12% and 80% [32].

Conventional imaging for CM-I includes MRI with T1-weighted magnetization prepared rapid gradient echo (MPRAGE) that allows visualisation of anatomical structures in details, like cerebral tonsils, as well as other sequences to visualize crowding at the foramen magnum (e.g. fast imaging employing steady state acquisition, FIESTA). Beside the tonsillar descent, MRI imaging allows defining also what has been called "complex Chiari" : brainstem herniation, dorsal medullary kink, retroflexion of the odontoid process, assimilation of C1, abnormal clival-axial angle, basilar invagination, syringomyelia, scoliosis can be all demonstrable on advanced imaging.

Other conditions that warrant imaging and can be associated with CM-I are hydrocephalus and all possible ventricular abnormalities, intracranial hypotension, intracranial hypertension, spinal dysraphism.

Roughly 1.5 mL of CSF is estimated to flow caudally across the foramen magnum at each systole, with some cranial rebound in diastole. This can be assessed with dedicated imaging that constitute the most advanced imaging studies for CM-I, namely cardiac gated phase contrast CSF flow (either on a midsagittal plane or on axial plane just below the tonsillar tip). This allows direct visualisation of pulsatile CSF flow at different moment of the cardiac cycle: while in normal individuals a balanced CSF flow is observed in both systole and diastole, in CM-I patients this equilibrium seems compromised and, when seen on a midsagittal plane, it seems decreased or even obstructed in the dorsal cistern around the tonsils or even ventrally. On axial plane studies, CM-I patients exhibit increased and bidirectional flow in the ventrolateral surface of the canal. Also, tonsillar motion (pulsatility) seems to be higher during the systole in patients with CM-I and extremely small or inexistent in normal individual: such pulsatility seems to decrease after surgical decompression [33]. However, these studies remain of very limited value: in fact, many studies have failed to show a consistent correlation between CSF flow and symptoms, or CSF flow and the degree of tonsillar herniation, or even CSF flow

and syrinx. Similarly, some children with symptomatic CM-I showed "normal values" of CSF flow at the foramen magnum and, as previously stated, yearly changes on tonsillar descent have been demonstrated without clinical significance in a prospective study [30]. This has led to question the actual value of follow-up imaging for CM-I.

4-CSF DISORDERS RELATED TO CHIARI I MALFORMATION (syringomyelia – idiopathic intracranial hypertension – CSF leaks and intracranial hypotension)

Neurosurgeons agree that a disruption of the normal CSF flow in and around the foramen magnum is a key component in CM-I, especially in the genesis of syringomyelia. The very first description of syringomyelia associated with CM-I dates back to 1881, when the German pathologist Theodor Langhans wrote about a case of cerebellar tonsils ectopia below the foramen magnum and a concurrent "fluid cyst" within the cervical spinal cord [34]: in his work he hypothesized an ischemic origin of the cavity related to an "increased pressure in the cerebellar cavity hindering or impeding the outflow of blood and cerebral spinal fluid". Other historical theories regarding syringomyelia formation and CM-I are ascribed to Gardner, (where the 4th ventricle behaves as a "water hammer" generated by the cardiac cycle pushing CSF through the obex and the central canal, expanding into a syrinx) or Williams (who suggested that the pulse wave of CSF is created during Valsalva manoeuvres and then forcing the CSF bulk from the intracranial cavity into the spinal canal). However, both theories implied the central canal being patent and opened, whereas subsequent autoptic studies showed that there are several occlusions of the central canal in individuals with and without syringomyelia, making it more of a regular finding. More recent studies have shown that syringomyelia is more likely to occur with a low-lying obex compared to a normal position , or with a reduced volume of the posterior fossa and crowding at the foramen magnum , or with intradural adhesions narrowing CSF pathways and the foramen of Magendie. All converges to a common feature of CSF flow disruption in and around the foramen magnum. Terminology about syringomyelia and CSF disorders varies widely in the literature. Here we adopt the following definitions[35]:

- *Syringomyelia*: fluid-filled cavity extending for more than one segment. Can be communicating (if it communicates with an enlarged 4th ventricle) or non - communicating (if it doesn't communicates with the 4th ventricle).
- *Hydromyelia*: a communicating syringomyelia with hydrocephalus

- *Extracanalicular syringomyelia*: a fluid filled cavity within the spinal cord parenchyma not communicating with the central ependymal canal nor the 4th ventricle.
- *Obex*: a thin layer of grey matter located 1-2mm posterior to the *apertura canalis centralis*, which is the opening of the central ependymal canal in the inferior part of the 4th ventricle. Of note, often the obex is assimilated to the *apertura canalis centralis*.

Modelling CSF dynamics across the foramen magnum has been based on fluid laminar flow, described by the Hagen-Poiseuille equation :

$$\Delta P = 8\mu LQ \,/\, \pi r^4$$

where:

- ΔP is the gradient of CSF pressure at both ends of the pipe, here the cranial and spinal compartments
- μ is the viscosity of the CSF
- L is the length of the pipe (here from the cranial compartment to the syringomyelia)
- Q is the volume of CSF per unit of time flowing in a laminar manner
- r is the radius of the pipe

Tonsillar ectopia reduces the surface (A) available for the laminar flow Q. Since the surface of a circle is $A = \pi r^2$, we can re-write the formula as

$\Delta P = 8\mu LQ\pi \,/\, \pi^2 r^4$, which is also $\Delta P = 8\mu LQ\pi \,/\, A^2$.

Since $8\mu L\pi$ can be considered constant, our equation can be simplified in

$$\Delta P = KQ \,/\, A^2$$

This means that half a reduction in the cross-sectional area of the cylinder (where the CSF flows) requires four times the pressure gradient at both ends to displace the volume of fluid per unit of time (Q). It is important to note that the Hagen-Poiseuille equation applies ideally to a laminar flow in cylindric pipes: in reality the CSF flow across the foramen magnum is oscillatory (depending on the cardiac and respiratory cycles) and is not purely laminar, but turbulent. Also, the geometry of the pipe is not simply cylindrical but annular (considering the dural sac, the CSF within the subarachnoid space, the cord parenchyma and the syrinx).

Nevertheless it helps us understanding how a cross section reduction of the area at the foramen magnum by the ectopic tonsils prevents dampening the CSF pressure pulse-wave from the intracranial compartment to the spinal compartment during cardiac systole. This increases the gradient of pressure (ΔP) across the foramen magnum (since the intracranial compartment has less compliance than the spinal compartment especially when the foramen magnum is crowded) and causes oscillatory displacement of parenchyma and CSF (caudally from the cranial cavity during systole and cranially during diastole). This pulsatile motion can be seen with ultrasounds during decompression procedures. The pressure pulse-wave is transferred during systole in the spinal subarachnoid space having possibly multiple effects on the CSF dynamics in the spinal compartment: propelling CSF directly within the spinal cord through the obex, or in the spinal arachnoid space (thus opposing the egression of CSF from the central canal through the glimphyatic system). Both mechanisms account for the craniocaudal and/or radial expansion of a syrinx [36]. The more accentuated pulsatility of the cerebellar/brain stem tissue at the foramen magnum in CM-I patients has been also described in phase contrast cine MRI. Decompression of the foramen magnum restore larger cross-sectional area and decreases the pressure gradient ΔP necessary to displace CSF between cranial and spinal compartments, improving the compliance of the posterior fossa. Beside similarities, hydrocephalus and syringomyelia are different in that in syringomyelia the expansion of the parenchyma involves primarily grey matter within the cord and the CSF produced within the cord is mainly extrachoroidal. In the brain, CSF is produced mostly by the choroid plexus. Also, there is autoptic evidence in humans of "normal stenosis" of the central canal, that tends to be more frequent in adults. This can account for the different sizes, extensions and locations of syringomyelia in CM-I (i.e. holosyrinx more frequent in children and central focal syringes in adults)[37]. The central canal is lined with ependyma and tanycytes that regulate water displacement with the extracellular compartment. At cellular level, Aquaporin 4 (AQP4) mediates the ingress of CSF from the arachnoid space to the cord parenchyma. AQP4 is also expressed by astrocytes around syrinx cavities, accounting also for normal interstitial fluid drainage across the cord parenchyma. Fluid accumulation within the syrinx can arise then from both CSF of the subarachnoid space and the extrachoroidal CSF locally produced through a transcapillary ionic gradient. Namely, extrachoroidal CSF production and retention can also explain why syrinx grow very slowly and can arise away from site of CSF blockage (foramen magnum). The predilection of syrinx for the lower cervical spine can also be explained by the fact that most of the extrachoroidal CSF production predominates withing grey matter, highly represented in the cervical spine.

After surgical decompression syrinx reduces over 3 to 6 months, further suggesting that the egress of CSF from within the cord to the spinal arachnoid space is a slow process. Other mechanisms support a slow process of syrinx formation due to limited capacity of the cord to drain excess interstitial fluid, for example in syrinx associated with tumours.

A subset of patient with CM-I can present with Idiopathic Intracranial Hypertension (IIH) , variably featured by headaches, papilledema, visual changes and pulsatile tinnitus due to elevated intracranial pressure. IIH commonly affect females in child-bearing age, with elevated body mass index (BMI) and/or abnormal levels of the steroid hormone estrone. Increased intraabdominal pressure with elevated BMI can increase central venous pressure (CVP) impairing CSF reabsorption. Estrone (product of conversion of androstenedione in adipocytes) can also stimulate CSF production. IIH has been also related to venous stenosis of dural sinus, especially in patients that did not respond to conservative treatment (like weight-loss or acetazolamide). However, it is unclear whether the stenosis is the trigger for IIH or is its consequence and according to some authors, there is high prevalence of dural stenosis in CM-I patients , suggesting a similar pathophysiology for both conditions. To demonstrate the high prevalence of dural venous stenosis in IIH, Farb and colleagues identified 93% of patients bearing this association (vs only 7% of controls) using magnetic resonance venography (MRV). Here patients develop chronic intracranial venous hypertension, contrasting the CSF absorption for which a pressure gradient of around 3-5 mmHg is normally required. Venous stenosis has been divided into extrinsic and intrinsic: extrinsic stenosis occurs because of the collapsibility of venous sinus (especially the transverse sinus) whereas intrinsic stenosis occur when intravenous structures (e.g. granulations, thrombi, fenestrations) hinder the normal blood flow. Extrinsic stenosis usually improves after ICP reduction, while intrinsic stenosis improves less. When high ICP is predominantly due to extracranial causes, venous stenting is less likely to improve this condition. A first description relating IIH and CM-I was proposed by Bejjani *et al.* in 2003, after 6 patients with CM-I failed to respond to foramen magnum decompression but improved after CSF shunting. In this subset of patients, tonsillar ectopia is merely a consequence of elevated ICP in the presence of craniocephalic disproportion and further reports have confirmed the same findings introducing the "*Chiari pseudotumor cerebri*" *syndrome*. The opposite has also been described for patients failing to respond to CSF diversion and responding to foramen magnum decompression, estimating tonsillar ectopia (CM-I) in 10-24% of patients with IIH [38]. According to another series, 33% of CM-I patients harbour transverse venous stenosis, regardless of age, sex or BMI. Similarly, coexistence of syndromic

craniosynostosis and venous stenosis seems to be predictive of tonsillar ectopia of CM-I. Potential co-existence of CM-I and IIH, when suspected (often after failure of foramen magnum decompression), should prompt complete workup for IIH, including venous sinus studies and/or ICP monitoring. ICP has been monitored before and after CM-I and has not shown a rapid normalization of both static and pulsatile values, which can explain why symptoms improve very slowly after posterior fossa decompression. Moreover, comparable elevated pulsatile ICP values have been found in both CM-I patients and IIH patients, suggesting in both cases an impaired intracranial compliance: of note, in the same cohort, static ICP values were higher in the IIH subgroup [39].

Radiological finding of CM-I can be encountered in CSF hypotension (or Spontaneous Intracranial Hypotension, SIH) due to spontaneous egress of CSF in the spinal compartment. This condition usually causes headaches worsened at upright position and/or at Valsalva manoeuvres, likely due to brain sagging from less buoyancy force driven by CSF onto the cerebral parenchyma. SIH can be attributed mainly to three mechanisms [40]:

- a tear in the spinal dura (usually due to osteophytes)
- a spinal nerve root sleeve diverticulum tear
- a CSF-venous fistula (usually located at a nerve root and without CSF collection in the epidural space)

The prevalence of SIH seems to be higher than previously thought, and it is estimated at 4 to 5 per 100,000 [41]. Aside from the upright position, headaches (its main clinical feature) can occur as well at Valsalva manoeuvres and/or associated with vestibulo-cochlear symptoms (dizziness, tinnitus, hypo/hyperacusia), facial symptoms, dysgeusia, diplopia (from cranial nerve traction due to brain sagging), hence partly overlapping with CM-I symptoms. In more severe cases, symptoms can arise from subdural collections (such has hygromas and/or subdural hematomas), as well as superficial siderosis. Despite its name, low CSF opening pressure can be hard to detect in such patients, thus radiographic criteria are key to a correct diagnosis. Imaging workup start usually with brain and spinal MRI followed – when needed – by more invasive procedures such as myelography and myelo-CT. Radiological findings include pachymeningeal enhancement, subdural collections, venous engorgement, brain sag, which can mimic tonsillar ectopia of CM-I. It is estimated that 20% of patients may have normal radiological findings. Partial overlapping between SIH and CM-I in clinical and radiological

findings has misled to foramen magnum decompressions procedures : however, in SIH headaches is often orthostatic and diffuse, while in CM-I is more at strain and localized at occiput or upper cervical spine. SIH tends to be more frequent in middle aged individuals, with CM-I often diagnosed in childhood, bearing in mind that both conditions can be found at any age. As opposed to posterior fossa crowding of CM-I, brain sagging in SIH can feature caudal shift of the midbrain and the third ventricular floor and flattening of the ventral pons and is rarely associated with syringomyelia (Table 2).

Table 2: Differences between SIH and CM-I , from Cerebrospinal Fluid leaks, spontaneous intracranial hypotension, and Chiari I malformation.

	SIH	**CM-I**
Epidemiology	Children to adults Middle aged women	Children to adults Symptomatic in early middle age
Pathophysiology	Spontaneous loss of CSF across spinal dura	Congenital crowding of posterior fossa
Presentation	Orthostatic and/or Valsalva headache Vestibulocochlear syndromes Frontotemporal dementia	Occipital-cervical headache aggravated by Valsalva Lower cranial nerve dysfunction Upper cervical cord syndromes Hydrocephalus
Imaging features	Brain sag Pachymeningeal enhancement Subdural fluid collections Cerebral sinus venous engorgement Rare Syrinx	Cerebellar tonsils descent below foramen magnum “peg like”/pointed tonsillar morphology Preservation of prepontine cistern Majority with syrinx
Treatment	Percutaneous epidural blood patch Microsurgical repair of spinal dural defect Transvenous embolization of CVF	Suboccipital craniectomy +/- expansion duroplasty

Hydrocephalus or CSF accumulation in the cranial compartment (with or without frank ventriculomegaly) can be unveiled after foramen magnum decompression, questioning the very first underlying process and its consequence (hydrocephalus or CM-I): by looking at how hydrocephalus was treated following more than 500 foramen magnum decompressions for CM-I, a personal study has suggested that both conditions can be cause and effect of the other. This involves either direct changes on the foramen magnum content after the decompression or pre-

existing conditions that went undiagnosed [42], including congenital aqueductal stenosis and foramina of Monro obstruction [43]. Pre-existing conditions in non-operated patients with CM-I, such as raised intracranial pressure ("pressure from above theory"), venous engorgement in craniosynostosis (from posterior fossa hypoplasia, jugular foramen stenosis, cerebellar oedema) or occlusion of basal cisterns or fourth ventricular outlets have been proposed as mechanisms to explain coexisting hydrocephalus and CM-I. This is the underlying reason to suggest endoscopic third-ventriculostomy (ETV) as an adequate option of treatment of tonsillar ectopia in selected patients before considering posterior fossa decompression. Interrelationships between cerebellar ectopia and other pathologies like hydrocephalus, tethered cord, brain tumour, occipito-cervical instability, can account for foramen magnum decompression failures and persistent, recurrent or progressing syringomyelia [44] and should therefore be ruled out before offering decompression. In all other cases a direct syrinx shunting can be offered [44,45] and when CM-I, syringomyelia and hydrocephalus co-exist, usually treating hydrocephalus with CSF diversion helps resolving the syrinx too. Parallel to the dispute about the aetiology of CM-I – syringomyelia complex, the persistence/recurrence/progression of syrinx after foramen magnum decompression is controversial matter, and has been related to various factors: further displacement of tonsils with obstruction of the cervicomedullary cisterns occluding the subarachnoid space, arachnoiditis, increased abdominal or thoracic pressure leading to an increased subarachnoid pressure. Generally speaking, elevated ICP seems to be associated with tonsillar ectopia and venous sinus stenosis seems associated with CM-I and IIH. To date, there is not a unifying theory to link all these phenomena: extracranial factors (e.g. elevated BMI) can lead to IIH, causing extrinsic venous sinus stenosis, causing in turn tonsillar ectopia. On the other hand, intrinsic venous sinus stenosis can cause elevated ICP, causing in turn extrinsic stenosis and tonsillar ectopia. Also, CSF abnormal dynamic in CM-I (without inciting extracranial factors nor intrinsic stenosis) can trigger elevated ICP and subsequent extrinsic stenosis. In all these models, there could be a positive feedback loop sustaining ICP elevation and symptoms.

5- SURGICAL ANATOMY AND TECHNICAL NUANCES FOR CHIARI I MALFORMATION

Despite a number of variants, the surgical treatment of CM-I involves posterior fossa decompression (PFD). This aims not only at direct decompression but also at re-establishing normal communication of CSF spaces between the cranial and spinal compartments, normalizing the craniospinal pressure dissociation.

PFD is reported in well 99% of the studies in the literature looking at surgical options for CM-I, and 92% advocate dural opening and duroplasty (PFDD). Variants in surgical techniques have been described for both adult, paediatric and combined populations. The opening of the dura and intradural work has been more often reported in adult and combined series than in paediatric-only series (72%, 70%, 47%, respectively) [46] on a large survey encompassing a period from 1965 to 2013.

Other variants include decompression without dural splitting, dural opening with arachnoid sparing, resection of tonsils and filum terminale, syringo-subarachnoid shunt, syringo-peritoneal shunt, all of which have not shown any significant superiority over PFD [47]. A subset of surgical treatment option is atlantoaxial fixation, as an alternative to PFD in cases where CM-I is considered secondary to instability and where the rationale involves an indirect enlargement of the posterior fossa by ventral decompression and dens distraction [48]. In another review, techniques using dural opening and duroplasty seemed associated to better symptoms improvements, syrinx reduction and reduced revision rate [49].

PFD/PFDD are commonly associated to C1 laminectomy (or more depending on the extent of the tonsillar ectopia) and removal of atlanto-occipital membrane.

When duroplasty is performed, the graft for dural augmentation can be autologous or non-autologous:

- autologous : usually pericranium, or nuchal ligament, or fascia lata
- non-autologous:
    - animal-based (bovine, porcine), made by acellular matrix of connective tissue
    - human-based (cadaveric dura, acellular dermal matrix)
    - synthetic, made by waterproof polymers (e.g. polytetrafluoroethylene)

There is no ultimate superiority of one graft over the others and the literature with this regard is sparse and inconclusive.

Comparing PFD and PFDD has been a common task in the literature looking at surgical outcomes for CM-I: overall, symptoms improvement after PFD or PFDD has been estimated

at 61-93% by a large metanalysis [50] and likely related to normalisation of CSF dynamics at the foramen magnum: indeed, according to one study, symptoms improvement was less likely to appear after surgery in patients with "normal" preoperative CSF dynamic studies. There is a trend to believe that PFDD has better control over syringomyelia reduction when compared to PFD (even though those reduction do not necessarily correlate with symptoms improvement). Understandably, complications rate for PFD has been reported by many studies at 12-24% whereas for PFDD seems to lie at 18-40%. Generally speaking, PFDD is associated with longer hospital stay, higher blood losses, longer operating times, and lower revision rates [51].
An ongoing randomized clinical trial (ClinicalTrial.gov NCT02669836) will probably yield the ultimate answer to the PFD vs PFDD controversy.

6- COMPLEX CHIARI MALFORMATION

A subset (and a minority) of patients will harbour tonsillar herniation along with other abnormalities that can variably involve ventral brain stem compression (VBC), craniovertebral junction (CVJ) instability and herniation of part of the brainstem through the foramen magnum, a picture now referred to as Complex Chiari Malformation (CCM).
Since the first description in 1891, it has become clear that the two main types of the malformation are CM-I and CM-II, with the most prevalent being CM-I. Only a small percentage (estimated 10 to 20%) will require surgical intervention (either PFD of PFDD) which resolves or improves the symptoms in up to 80% of patients. Of these, only a small proportion (1.6% in a series of 637 patients) may require further surgery (ventral decompression and/or occipito-cervical fusion, OCF [52]. These patients fall mainly into three categories:

- patients with CVJ instability
- patients who do not improve after PFD (or PFDD) alone and develop CVJ
- patients who improve after PFD (or PFDD) and subsequently develop brainstem compression symptoms without overt CVJ instability

The whole subset of these conditions was described and defined as CCM in 2011 by Brockmeyer [53]. The osteo-ligementous structures of the CVJ are complex and their fine description is beyond the scope of this monograph. Abnormalities of the osteo-ligamentous structures of the CVJ that can cause instability and/or VBC are schematically [54]:

- Condylar Hypoplasia (CH): the "ball and cup" shape of the occipital condyle-superior C1-joint facets physiologically limit translation and axial rotation and allow flexion/extension. C0C1 joint allows around 25° of flexion/extension and only 7° rotation. When hypoplasia occur, occipital condyle are flatter and shorter and will produce antero-posterior translation: this can result in occipital-C1 pannus +/- basilar invagination (BI)
- Atlas Assimilation (AA): a congenital fusion of the atlas with the basiocciput due to segmentation failure. In normal conditions C1C2 complex allows 10 to 22° flexion/extension and 40° rotation. AA prevents occipital-C1 flexion/extension thus placing mechanical stress on C1C2 joints. This can result in C1C2 instability, as well as developmental or true BI (see below)
- C2C3 segmentation failure: a congenital fusion of C2C3 (within a Klippel-Feil syndrome - if other spinal segments are involved - or isolated - in which case is termed Klippel-Feil abnormality) that will place stress over C1C2 joints and which can result in C1C2 instability with increased atlantoaxial interval (ADI) and true BI
- Basilar Invagination: is usually defined when the odontoid process lies less then 5mm above the Chamberlain's line (hard palate to opisthion). It can be:

  developmental, i.e. associated with CH or AA and not to C1C2 instability and in these cases the odontoid may not be invaginated within the FM but still lies less than 5mm above the Chamberlain's line

  true, i.e. associated with C1C2 instability and/or C2 vertical subluxation within the foramen magnum
- Basilar impression: it usually refers to an acquired form of BI related to softening of the skull base (i.e. Paget disease, osteogenesis imperfecta etc.).
- Retroflexed odontoid: in isolated cases this doesn't necessarily produce instability nor BI , whereas when associated with CH or AA can participate to VBC
- Proatlas segmentation abnormalities
- Bifid anterior or posterior C1 arch with instability
- Os odontoideum with instability

All these abnormalities can be isolated or within a syndrome (e.g. muchopolysaccharidosis VI, VACTERL syndrome, Klippel Feil syndrome, Osteogenesis imperfecta, Apert's, etc).

Clinical presentations of CCM – the main factor for the decision making process in such patients – is variable. Usually children younger than 4 present with oropharyngeal problems (sleep apnoea, snoring, dysphagia), followed by Valsalva-induced occipital headaches and a number of localising neurological signs due to brainstem or spinal cord compression / syringomyelia, including scoliosis. Myelopathy seems to be the most common finding in children with CVJ instability, along with hearing loss from cranial nerves involvement. Despite the rarity of such abnormalities in patients with tonsillar ectopia, imaging (MRI, CT and plain/dynamic X-ray) should also look at CVJ anatomy and assess specific findings.

It is important to differentiate vertical from translational instability at the CVJ (the former being more frequent in CM-I and the latter being more often traumatic or syndromic). There is not universal agreement on the radiographic findings to define CVJ instability and ventral compression, hence the radiological parameters that have been developed are not to be taken dogmatically and have to be integrated to the clinical picture and history of the single patient. At present time, and following a number of series looking at such abnormalities in order to define the CCM (and thus the need for additional surgical work) it seems that the best indicators for CCM are[55] :

- pBC2 line (maximum perpendicular distance to the basion-inferoposterior corner of C2): when greater than 9 mm is considered to be abnormal and related to odontoid retroflexion and need for OCF
- CXA (clivo-axial angle): it is used to determine the relationship between the skull and the C-spine. It is defined by the angle formed by the intersection of a line drawn along the clivus and a line drawn along the posterior aspect of the odontoid. It normally varies between 144° (in flexion) and 170° (in extension) and it is considered abnormal when less than 125° (kyphotic).
- C-C2 SVA (condyle – C2 sagittal vertical axis): measured on C2 endplate (on sagittal cut) and C0C1 joint midpoint (on parasagittal cut) from where a perpendicular line is drawn. The distance between the posterior point of C2C3 disc and the intersection between the plumb line is measured. It is considered abnormal when greater than 5mm.
- Projection of the odontoid tip above the McRae's line, to define the extent of basilar invagination (normally 5 mm below the Mc Rae's line). This can indicate need for occipitocervical fusion [56].

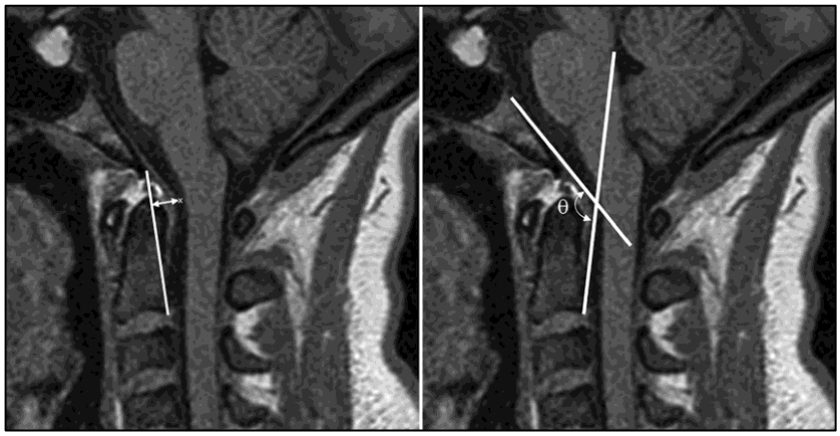

Fig 7: pBC2 distance (right) and CXA (left)

When facing CCM, a number of factors has be taken into account for choosing the surgical strategy, namely:

- the reducibility of the abnormality with restoration of normal anatomy
- the direction of the compression on neural structures
- the presence of overt CVJ instability
- the extent of tonsillar herniation and/or syringomyelia

Reducible anatomical abnormality with VBC can be treated with preoperative crown-halo traction, with/without intraoperative distraction and followed by PFD (or PFDD) and OCF [57], whereas irreducible abnormalities may require ventral decompression (endonasal or transoral if above the hard palate – transoral or transcervical if below the hard palate), followed by PFD (or PFDD) and OCF. Improvements in occipito-cervical instrumentation, intraoperative imaging and monitoring as well as better understanding of CVJ pathophysiology have decreased the need of ventral approaches for decompression and allowed to resolve most cases with posterior approaches, combining decompression, intraoperative distraction/reduction and stabilisation/fusion altogether.

7- CHIARI I MALFORMATION, SPINAL DEFORMITY AND SYRINGOMYELIA

Association with CM-I and scoliosis is well understood and reported, and averages 20% : it becomes higher (30-70%) when CM-I is also associated to syringomyelia [58].

The most accredited theory holds that syringomyelia alters the innervation of paraspinal muscle originating from anterior horns of the spinal cord whereas - for CM-I without syringomyelia - another theory suggests that tonsillar ectopia may cause direct brainstem compression altering postural tonic reflexes to the spine leading to the deformity [59]: for this reason scoliosis in CM-

I patients can be regarded as *neuromuscular*, even though different from other neuromuscular disorders (e.g. cerebral palsy, spinal dysraphism etc.).

There is limited evidence about natural history and treatment options of spinal deformity associated with CM-I (with or without syringomyelia), coming from sparse and heterogenous series. Scoliosis is defined by a coronal Cobb angle greater than 20° at any level of the spine and can be detected by a positive Adam forward bend test, as well as presented as a cosmetic complaint by children or their parents.

Aside from obvious spinal deformity visible at clinical examination, whenever clinical suspicion is raised (oropharyngeal problems, back pain, absence/asymmetry of cutaneous-abdominal reflexes) a whole spine MRI should be obtained to detect neural abnormalities , regardless of the age of the child. Children presenting with idiopathic scoliosis at less than 10 years of age should also undergo MRI of the whole spine, since spinal cord abnormalities seems highly probable. On the other hand, the simple presence of syringomyelia with CM-I seems to increase the risk of spinal deformity and according to some studies the extent of the syringomyelia positively correlates with a risk of scoliosis onset [60]: despite the lack of evidence for the screening of scoliosis, whether children are younger or older than 10, there is increasing trend to order radiographic studies to detect juvenile/adolescent spinal deformity.

Early diagnosis and treatment of CM-I could result in spinal deformity stability or regression and the reported improvement after PFD is variable, with 18 – 70% of patients still requiring spinal instrumentation and fusion [60].

In CM-I patients, when scoliosis is associated with syringomyelia, there seems to be no controversy on proceeding to PFD or PFDD. There are speculations about the superiority of PFDD vs PFD at reducing syringomyelia and subsequently scoliosis, due to a better restoring of CSF dynamic at the foramen magnum. Overall, early decompression, younger age, smaller curve at the moment of PFD/PFDD and greater syringomyelia resolution seem to be associated with curve stabilisation and/or regression without the need of spinal instrumentation[60].

Patients with CM-I and scoliosis but without syringomyelia may not require surgical treatment of the posterior fossa further stressing the importance of syringomyelia on curve progression rather than the tonsillar herniation.

8- DISCUSSION AND CLINICAL PERSPECTIVES (towards a unified practice of Chiari Malformations)

The current knowledge about Chiari Malformations seems to expand towards different mechanisms rather than to a common origin. In fact, the variety of mechanisms leading to a longstanding cerebellar tonsils ectopia and its clinical manifestations can somewhat hinder a simple unified theory to explain all the possible clinical manifestations. On the other hand, if we were to see the cerebellar tonsils ectopia only as a common point between different pathophysiological mechanisms, we can accept the provocative statement that Chiari Malformations do not exist as such. In this sense, when facing symptomatic low-lying tonsils we should first ask ourselves what is the mechanisms behind such a condition. In this regard, the "true" CM-I would be only a minority of the cases seen and would correspond to symptomatic low-lying tonsils where no other obvious mechanism has been found and that is related to a cranio-cephalic disproportion of the posterior fossa of mesodermal origin.

A unified theory should be more of a practical value to the clinician dealing with a symptomatic patient, a mental framework to understand the correct pathophysiology and adequate treatment for a given patient. A few key concepts of such a unified practice for cerebellar tonsils ectopia can be summarized below:

Clinical diagnostic:

First, in the clinical setting is important to:

- distinguish incidental CM-I from symptomatic CM-I
- identify associated features of CM-I (e.g. scoliosis, syringomyelia)
- identify possible other causes of tonsillar herniation and associated conditions (e.g. tumors, craniosynostosis, idiopathic intracranial hypertension, intracranial hypotension, lumboperitoneal shunting, hydrocephalus, lumbosacral dysraphisms, Ehlers Danlos syndrome type 3, Neurofibromatosis type I, craniovertebral junction abnormalities, growth hormone deficiency).

Second, when a patient is presenting with headaches, some aspects are clinically relevant to suspect these headaches related to tonsillar ectopia, namely: *evidence of posterior fossa crowding* (tonsillar herniation or effacement of subarachnoid space at the cervicomedullary junction), *common headaches characteristics*, *presence of associated symptoms* (dizziness, change in sensory functions, scoliosis, symptoms from compression of neural structures at the cervicomedullary junction).

Radiologic assessment:

First: one must bear in mind that the 5 mm cut-off of caudal displacement of the tonsils is an arbitrary definition, it doesn't always correlate with symptoms, and most importantly there is a normal variation of the position of the tonsils in a given population as well as over the course of an individual life.

Second: some radiological features in low-lying tonsils consistently correlate with decision to surgery, even for asymptomatic patients, namely the coexistence of CM-I and syringomyelia and the coexistence of scoliosis and cerebellar ectopia, since both conditions are reported to respond well to surgical decompression.

Third: practical radiological parameters that have been robustly related to CVJ instability and/or VBC are[55]:

- The presence of CM 1.5 (tonsillar *and* brainstem descent through the foramen magnum – and not fourth ventricle)
- CXA (clivo-axial angle) < 125°
- C-C2 SVA (sagittal vertical axis) > 5 mm
- pBC2 distance > 9mm

9- CONCLUSIONS

Chiari malformations and particularly the most represented one, CM-I, still remain a matter of debate on nearly every aspects, from its true incidence and prevalence to its pathophysiology and treatment. To complicate the matter more, there is lack of strong evidence in the literature and most of the theories and the clinical practice rely on observational studies.

The current bulk of knowledge allows to disentangle what has always been called CM-I into at least three aspects, each one with direct consequences on the diagnostic and therapeutic choices:

- posterior fossa disproportion (from mesodermal origin)
- CSF impairment between cranial and spinal compartments
- CVJ instability

Despite the several thousands of papers published since 1891, it is impossible to base the current clinical practice on strong evidence from randomized controlled trials, which often focus on evaluating the efficacy of a single intervention under controlled conditions. Evidence about CM-I will be derived most likely by comparative effectiveness research - comparing one (or more) treatment(s) to determine what works best for which patients under real world settings.

REFERENCES

1. Chiari H. Ueber Veranderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns *Deutsche Medizinische Wochenschrift* 1891;17:1172-5.
2. Tubbs RS, Cohen-Gadol AA. Hans Chiari (1851-1916). *J Neurol*. 2010;257(7):1218-20. doi:10.1007/s00415-010-5529-0
3. Azahraa Haddad F, Qaisi I, Joudeh N, et al. The newer classifications of the chiari malformations with clarifications: An anatomical review. *Clin Anat*. 2018;31(3):314-322. doi:10.1002/ca.23051
4. Carmel PW, Markesbery WR. Early descriptions of the Arnold-Chiari malformation. The contribution of John Cleland. *J Neurosurg*. 1972;37(5):543-7. doi:10.3171/jns.1972.37.5.0543
5. Barkovich AJ, Wippold FJ, Sherman JL, Citrin CM. Significance of cerebellar tonsillar position on MR. *AJNR Am J Neuroradiol*. 1986;7(5):795-9.
6. Aitken LA, Lindan CE, Sidney S, et al. Chiari type I malformation in a pediatric population. *Pediatr Neurol*. 2009;40(6):449-54. doi:10.1016/j.pediatrneurol.2009.01.003
7. Iskandar BJ, Hedlund GL, Grabb PA, Oakes WJ. The resolution of syringohydromyelia without hindbrain herniation after posterior fossa decompression. *J Neurosurg*. 1998;89(2):212-6. doi:10.3171/jns.1998.89.2.0212
8. Chern JJ, Gordon AJ, Mortazavi MM, Tubbs RS, Oakes WJ. Pediatric Chiari malformation Type 0: a 12-year institutional experience. *J Neurosurg Pediatr*. 2011;8(1):1-5. doi:10.3171/2011.4.Peds10528
9. Morgenstern PF, Tosi U, Uribe-Cardenas R, Greenfield JP. Ventrolateral Tonsillar Position Defines Novel Chiari 0.5 Classification. *World Neurosurg*. 2020;136:444-453. doi:10.1016/j.wneu.2020.01.147
10. Tubbs RS, Iskandar BJ, Bartolucci AA, Oakes WJ. A critical analysis of the Chiari 1.5 malformation. *J Neurosurg*. 2004;101(2 Suppl):179-83. doi:10.3171/ped.2004.101.2.0179
11. McLone DG, Naidich TP. Developmental morphology of the subarachnoid space, brain vasculature, and contiguous structures, and the cause of the Chiari II malformation. *AJNR Am J Neuroradiol*. 1992;13(2):463-82.
12. Bollo RJ, Riva-Cambrin J, Brockmeyer MM, Brockmeyer DL. Complex Chiari malformations in children: an analysis of preoperative risk factors for occipitocervical fusion. *J Neurosurg Pediatr*. 2012;10(2):134-41. doi:10.3171/2012.3.Peds11340
13. Tubbs R, Oaks W. *The Chiari Malformations* 1st ed. Springer 2013.
14. McLone DG, Dias MS. The Chiari II malformation: cause and impact. *Childs Nerv Syst*. 2003;19(7-8):540-50. doi:10.1007/s00381-003-0792-3
15. Blount JP. *The Chiari Malformations*. 1st ed. Springer 2013.
16. Grabb PA, Vlastos EJ, Lundy PA, Partington MB. Significant brainstem dysfunction in neonates with myelomeningoceles: a comparison of prenatal versus postnatal closure. *J Neurosurg Pediatr*. 4 2022:1-7. doi:10.3171/2021.12.Peds21430
17. Elbaroody M, Mostafa HE, Alsawy MFM, Elhawary ME, Atallah A, Gabr M. Outcomes of Chiari Malformation III: A Review of Literature. *J Pediatr Neurosci*. 2020;15(4):358-364. doi:10.4103/jpn.JPN_135_19
18. Fisahn C, Shoja MM, Turgut M, Oskouian RJ, Oakes WJ, Tubbs RS. The Chiari 3.5 malformation: a review of the only reported case. *Childs Nerv Syst*. 2016;32(12):2317-2319. doi:10.1007/s00381-016-3255-3

19. Shoja MM, Ramdhan R, Jensen CJ, Chern JJ, Oakes WJ, Tubbs RS. Embryology of the craniocervical junction and posterior cranial fossa, part II: Embryogenesis of the hindbrain. *Clin Anat*. 2018;31(4):488-500. doi:10.1002/ca.23048
20. Shoja MM, Ramdhan R, Jensen CJ, Chern JJ, Oakes WJ, Tubbs RS. Embryology of the craniocervical junction and posterior cranial fossa, part I: Development of the upper vertebrae and skull. *Clin Anat*. 2018;31(4):466-487. doi:10.1002/ca.23049
21. Shoja MM, Johal J, Oakes WJ, Tubbs RS. Embryology and pathophysiology of the Chiari I and II malformations: A comprehensive review. *Clin Anat*. 2018;31(2):202-215. doi:10.1002/ca.22939
22. Atallah O, Wolff Fernandes F, Krauss JK. The Chiari Malformations: A Bibliometric Analysis of the 100 Most Cited Articles. *World Neurosurg*. 2023;175:e754-e768. doi:10.1016/j.wneu.2023.04.015
23. Milhorat TH, Chou MW, Trinidad EM, et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. *Neurosurgery*. 1999;44(5):1005-17. doi:10.1097/00006123-199905000-00042
24. Goel A. Is atlantoaxial instability the cause of Chiari malformation? Outcome analysis of 65 patients treated by atlantoaxial fixation. *J Neurosurg Spine*. 2015;22(2):116-27. doi:10.3171/2014.10.Spine14176
25. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *N Engl J Med*. 1 2007;357(18):1821-8. doi:10.1056/NEJMoa070972
26. Smith BW, Strahle J, Bapuraj JR, Muraszko KM, Garton HJ, Maher CO. Distribution of cerebellar tonsil position: implications for understanding Chiari malformation. *J Neurosurg*. 2013;119(3):812-9. doi:10.3171/2013.5.Jns121825
27. Ciaramitaro P, Garbossa D, Peretta P, et al. Syringomyelia and Chiari Syndrome Registry: advances in epidemiology, clinical phenotypes and natural history based on a North Western Italy cohort. *Ann Ist Super Sanita*. 2020;56(1):48-58. doi:10.4415/ann_20_01_08
28. Strahle J, Muraszko KM, Kapurch J, Bapuraj JR, Garton HJ, Maher CO. Chiari malformation Type I and syrinx in children undergoing magnetic resonance imaging. *J Neurosurg Pediatr*. 2011;8(2):205-13. doi:10.3171/2011.5.Peds1121
29. Krucoff MO, Cook S, Adogwa O, et al. Racial, Socioeconomic, and Gender Disparities in the Presentation, Treatment, and Outcomes of Adult Chiari I Malformations. *World Neurosurg*. 2017;97:431-437. doi:10.1016/j.wneu.2016.10.026
30. Whitson WJ, Lane JR, Bauer DF, Durham SR. A prospective natural history study of nonoperatively managed Chiari I malformation: does follow-up MRI surveillance alter surgical decision making? *J Neurosurg Pediatr*. 2015;16(2):159-66. doi:10.3171/2014.12.Peds14301
31. Milhorat TH, Nishikawa M, Kula RW, Dlugacz YD. Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management. *Acta Neurochir (Wien)*. 2010;152(7):1117-27. doi:10.1007/s00701-010-0636-3
32. Jussila MP, Nissilä J, Vakkuri M, et al. Preoperative measurements on MRI in Chiari 1 patients fail to predict outcome after decompressive surgery. *Acta Neurochir (Wien)*. 2021;163(7):2005-2014. doi:10.1007/s00701-021-04842-y
33. Sharma A, Parsons MS, Pilgram TK. Balanced steady-state free-precession MR imaging for measuring pulsatile motion of cerebellar tonsils during the cardiac cycle: a reliability study. *Neuroradiology*. 2012;54(2):133-8. doi:10.1007/s00234-011-0861-3

34. Mortazavi MM, Tubbs RS, Brockerhoff MA, Loukas M, Oakes WJ. The first description of Chiari I malformation with intuitive correlation between tonsillar ectopia and syringomyelia. *J Neurosurg Pediatr*. 2011;7(3):257-60. doi:10.3171/2010.12.Peds10579
35. Milhorat TH. Classification of syringomyelia. *Neurosurg Focus*. 15 2000;8(3):E1. doi:10.3171/foc.2000.8.3.1
36. Heiss JD, Patronas N, DeVroom HL, et al. Elucidating the pathophysiology of syringomyelia. *J Neurosurg*. 1999;91(4):553-62. doi:10.3171/jns.1999.91.4.0553
37. Milhorat TH, Kotzen RM, Anzil AP. Stenosis of central canal of spinal cord in man: incidence and pathological findings in 232 autopsy cases. *J Neurosurg*. 1994;80(4):716-22. doi:10.3171/jns.1994.80.4.0716
38. Aiken AH, Hoots JA, Saindane AM, Hudgins PA. Incidence of cerebellar tonsillar ectopia in idiopathic intracranial hypertension: a mimic of the Chiari I malformation. *AJNR Am J Neuroradiol*. 2012;33(10):1901-6. doi:10.3174/ajnr.A3068
39. Frič R, Eide PK. Comparative observational study on the clinical presentation, intracranial volume measurements, and intracranial pressure scores in patients with either Chiari malformation Type I or idiopathic intracranial hypertension. *J Neurosurg*. 2017;126(4):1312-1322. doi:10.3171/2016.4.Jns152862
40. Schievink WI, Maya MM, Jean-Pierre S, Nuño M, Prasad RS, Moser FG. A classification system of spontaneous spinal CSF leaks. *Neurology*. 16 2016;87(7):673-9. doi:10.1212/wnl.0000000000002986
41. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202
42. Bartoli A, Soleman J, Berger A, et al. Treatment Options for Hydrocephalus Following Foramen Magnum Decompression for Chiari I Malformation: A Multicenter Study. *Neurosurgery*. 1 2020;86(4):500-508. doi:10.1093/neuros/nyz211
43. Bartoli A, Ghinda CD, Radovanovic I, Momjian S. Hidden aqueductal stenosis associated to bilateral idiopathic foramina of Monro stenosis mimicking a Chiari I malformation? Case report. *Acta Neurochir (Wien)*. 2012;154(11):2109-13; discussion 2113. doi:10.1007/s00701-012-1438-6
44. Soleman J, Bartoli A, Korn A, Constantini S, Roth J. Treatment failure of syringomyelia associated with Chiari I malformation following foramen magnum decompression: how should we proceed? *Neurosurg Rev*. 2019;42(3):705-714. doi:10.1007/s10143-018-01066-0
45. Soleman J, Roth J, Bartoli A, Rosenthal D, Korn A, Constantini S. Syringo-Subarachnoid Shunt for the Treatment of Persistent Syringomyelia Following Decompression for Chiari Type I Malformation: Surgical Results. *World Neurosurg*. 2017;108:836-843. doi:10.1016/j.wneu.2017.08.002
46. Arnautovic A, Splavski B, Boop FA, Arnautovic KI. Pediatric and adult Chiari malformation Type I surgical series 1965-2013: a review of demographics, operative treatment, and outcomes. *J Neurosurg Pediatr*. 2015;15(2):161-77. doi:10.3171/2014.10.Peds14295
47. Antkowiak L, Tabakow P. Comparative Assessment of Three Posterior Fossa Decompression Techniques and Evaluation of the Evidence Supporting the Efficacy of Syrinx Shunting and Filum Terminale Sectioning in Chiari Malformation Type I. A Systematic Review and Network Meta-Analysis. *World Neurosurg*. 2021;152:31-43. doi:10.1016/j.wneu.2021.05.124

48. Goel A, Jadhav D, Shah A, et al. Chiari 1 Formation Redefined-Clinical and Radiographic Observations in 388 Surgically Treated Patients. *World Neurosurg*. 2020;141:e921-e934. doi:10.1016/j.wneu.2020.06.076
49. Akbari SHA, Yahanda AT, Ackerman LL, et al. Complications and outcomes of posterior fossa decompression with duraplasty versus without duraplasty for pediatric patients with Chiari malformation type I and syringomyelia: a study from the Park-Reeves Syringomyelia Research Consortium. *J Neurosurg Pediatr*. 15 2022:1-13. doi:10.3171/2022.2.Peds21446
50. Xu H, Chu L, He R, Ge C, Lei T. Posterior fossa decompression with and without duraplasty for the treatment of Chiari malformation type I-a systematic review and meta-analysis. *Neurosurg Rev*. 2017;40(2):213-221. doi:10.1007/s10143-016-0731-x
51. Yahanda AT, Limbrick DD, Jr. Posterior Fossa Decompression with or Without Duraplasty for Chiari I Malformation. *Neurosurg Clin N Am*. 2023;34(1):105-111. doi:10.1016/j.nec.2022.08.008
52. CreveCoeur TS, Yahanda AT, Maher CO, et al. Occipital-Cervical Fusion and Ventral Decompression in the Surgical Management of Chiari-1 Malformation and Syringomyelia: Analysis of Data From the Park-Reeves Syringomyelia Research Consortium. *Neurosurgery*. 13 2021;88(2):332-341. doi:10.1093/neuros/nyaa460
53. Brockmeyer DL. The complex Chiari: issues and management strategies. *Neurol Sci*. 2011;32 Suppl 3:S345-7. doi:10.1007/s10072-011-0690-5
54. Dlouhy BJ, Menezes AH. Management of Ventral Brainstem Compression in Chiari Malformation Type I. *Neurosurg Clin N Am*. 2023;34(1):119-129. doi:10.1016/j.nec.2022.08.002
55. Ravindra VM, Brockmeyer DL. Complex Chiari Malformations: Diagnosis, Evaluation, and Treatment. *Neurosurg Clin N Am*. 2023;34(1):143-150. doi:10.1016/j.nec.2022.08.009
56. Ho WSC, Brockmeyer DL. Complex Chiari malformation: using craniovertebral junction metrics to guide treatment. *Childs Nerv Syst*. 2019;35(10):1847-1851. doi:10.1007/s00381-019-04214-z
57. Jannelli G, Moiraghi A, Paun L, Tessitore E, Dayer R, Bartoli A. Severe Basilar impression in osteogenesis imperfecta treated with halo gravity traction, occipitocervicothoracic fusion, foramen magnum and upper cervical decompression and expansive duroplasty: a technical note. *Childs Nerv Syst*. 2022;38(5):991-995. doi:10.1007/s00381-022-05495-7
58. Strahle JM, Taiwo R, Averill C, et al. Radiological and clinical associations with scoliosis outcomes after posterior fossa decompression in patients with Chiari malformation and syrinx from the Park-Reeves Syringomyelia Research Consortium. *J Neurosurg Pediatr*. 10 2020;26(1):53-59. doi:10.3171/2020.1.Peds18755
59. Batzdorf U, McArthur DL, Bentson JR. Surgical treatment of Chiari malformation with and without syringomyelia: experience with 177 adult patients. *J Neurosurg*. 2013;118(2):232-42. doi:10.3171/2012.10.Jns12305
60. Strahle JM, Taiwo R, Averill C, et al. Radiological and clinical predictors of scoliosis in patients with Chiari malformation type I and spinal cord syrinx from the Park-Reeves Syringomyelia Research Consortium. *J Neurosurg Pediatr*. 16 2019:1-8. doi:10.3171/2019.5.Peds18527

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