Universitat de Girona
Facultat de Medicina

Final Degree Project:

Predicting postoperative outcomes in adults with Chiari I malformation clinically presenting with atypical headache by means of brainstem fractional anisotropy values.

A PROGNOSTIC TEST ACCURACY STUDY

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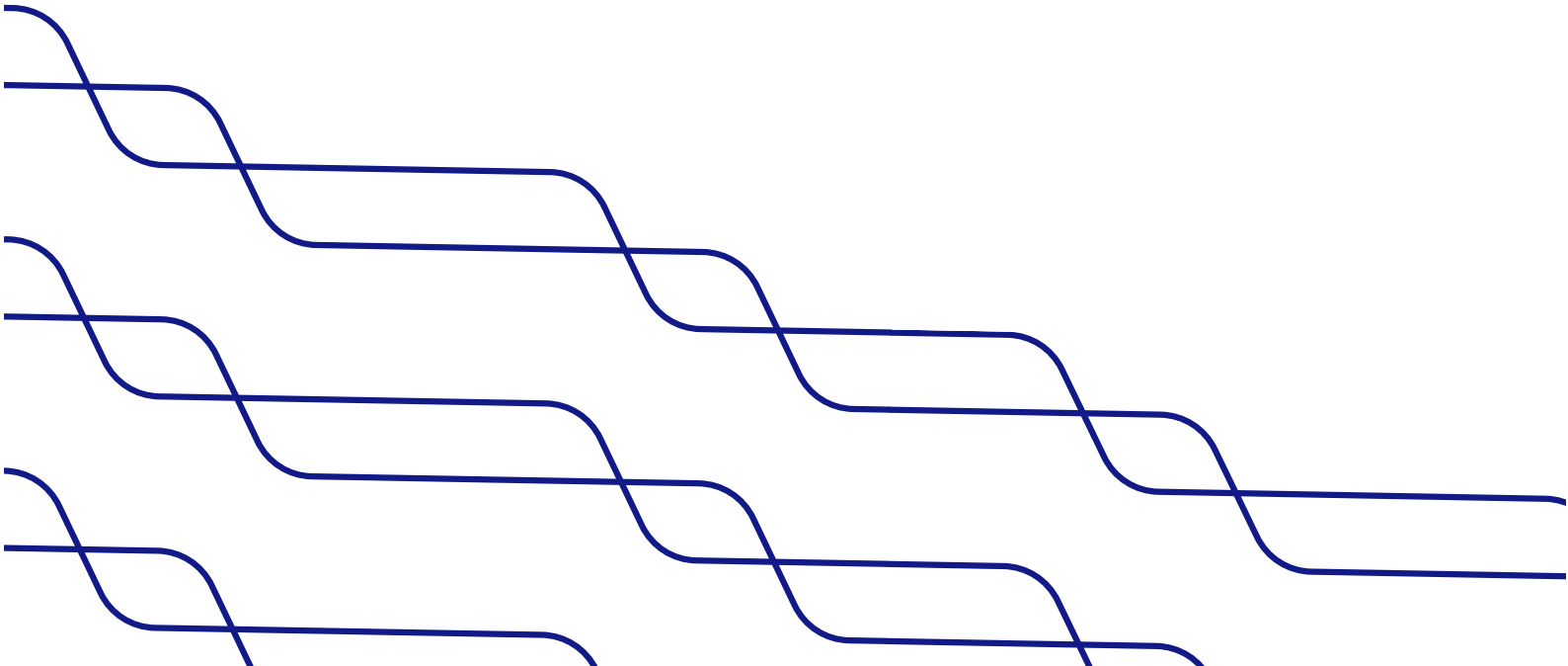

AGRAÏMENTS:

M'agradaria començar a agrair a tota aquella gent que ha fet possible que aquest treball es dugui a terme:

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"Where the art of medicine is loved, there is also love for humanity".

Hippocrates.

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ACRONYMS AND ABBREVIATIONS

ACS	Arnold Chiari Syndrome
AD	Axial Diffusivity
ADC	Axial Diffusion Coefficient
CCOS	Chicago Chiari Outcome Scale
CIM	Chiari I Malformation
CIIM	Chiari II Malformation
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed tomography
DE	Diagnostic Efficiency
DTI	Diffusion Tensor Imaging
FA	Fractional anisotropy
FT	Fiber tractography
HUAdV	Hospital Universitari Arnau de Vilanova
HUGTiP	Hospital Universitari Germans Trias i Pujol
HUJT	Hospital Universitari Josep Trueta
IHS	International Headache Society
LR	Likelihood Ratio
MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
PFD	Posterior fossa decompression
PPV	Positive Predictive Value
RD	Radial Diffusivity
ROC curve	Receiver Operating Characteristic curve
ROI	Region of interest
VAS	Visual Analogue Scale
WM	White matter

ABSTRACT

TITLE: Predicting postoperative outcomes in adults with Chiari I malformation clinically presenting with atypical headache by means of brainstem fractional anisotropy values.

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BACKGROUND: There is no clear consensus about the precise algorithm for the management of Chiari I malformation (CIM), specially, in patients presenting clinically an atypical headache. The brainstem is one of the most compromised areas in CIM due to the compression exerted by tonsillar migration. Posterior fossa decompression (PFD) leads to an increase in space and the alleviation of pressure on the spinal cord. Hence, our question is whether measuring fractional anisotropy (FA) values in the brainstem could predict surgical response in patients with CIM presenting an atypical headache.

OBJECTIVES: To evaluate the sensitivity of having higher brainstem fractional anisotropy values as a predictor of good surgical outcomes in patients with CIM clinically presenting with atypical headache.

DESIGN AND METHODS: The research is designed as a non-experimental longitudinal study, observing brainstem FA results of patients with CIM presenting atypical headache. Presurgical and postsurgical pain evaluation will be measured with the visual analogue scale (VAS) and the respective results will be compared to assess improvement or not. The sensitivity of having higher brainstem FA results to predict good surgical outcome will be evaluated along with other measurements: specificity, positive and negative predictive values, ROC curve, likelihood ratio and the diagnostic accuracy.

STUDY PARTICIPANTS: 39 patients with CIM suffering from an atypical headache will be recruited from the presurgical consultation in Hospital Universitari Josep Trueta (Girona), Hospital Unversitari Germans Trias i Pujol (Badalona) and Hospital Universitari Arnau de Vilanova (Lleida).

KEYWORDS: Chiari I malformation; atypical headache; brainstem; posterior fossa decompression; fractional anisotropy; sensitivity; good surgical outcome; visual analogue scale.

1. INTRODUCTION

1.1. ARNOLD CHIARI MALFORMATION

1.1.1. INTRODUCTION

Arnold Chiari Syndrome (ACS) is defined as a group of posterior fossa and hindbrain malformations, including cerebellum, pons and medulla oblongata, which usually occurs when the lower surface of the cerebellum and sometimes lower brainstem herniates through the foramen magnum into the spinal canal. These malformations often lead to alterations in cerebrospinal fluid (CSF) dynamics and can be associated to a range of intracranial and extracranial complications such as hydrocephalus, spinal cord syrinx, encephalocele or spinal dysraphism (1).

Furthermore, ACS is often a challenging malformation when it comes to treatment decision, as the clinical presentation is often really unspecific; therefore, symptoms in many patients do not improve or even get worse after the surgical intervention. So, it is not clear if all symptomatic patients should be undergoing surgery.

Last but not least, it is important to consider that ACS is not a life-threatening malformation. However, patients refer to experience painful headaches and other symptoms which interfere in their daily lives and therefore, in their quality of life.

1.1.2. CLASSIFICATION

ACS is classified classically into 4 different groups depending on the morphology and severity of anatomic demonstrated tipically by magnetic resonance imaging (MRI) (1).

- **Chiari I malformation (CIM):** it is the most frequent group and also the least severe, and it is characterized by caudal displacement of cerebellar tonsils of 5mm or greater below the foramen magnum. However, when there is a displacement between 3-5mm it is known as a borderline to develop CIM. In some cases, this malformation is followed by the formation of syringomyelia and hydrocephalus due to the obstruction of CSF flow produced by the anormal displacement.

- **Chiari II malformation (CIIM):** it is more complex than CIM and it is characterized by herniation of cerebellar tonsils, vermis and brainstem (2).The tonsils tend to be both pointed instead of rounded. It is more frequent in infants and often is associated with hydrocephalus and myelomeningocele (seen as a sac on patients' low back).
- **Chiari III:** consists of herniation of the cerebellum and brainstem typically into a posterior encephalocele, which is a protrusion of the encephalus and the membranes that cover it (typically seen as a sac on patients' back).
- **Chiari IV:** it is the rarest variant which is now obsolete, and it refers to cerebellar and tentorium hypoplasia or aplasia.

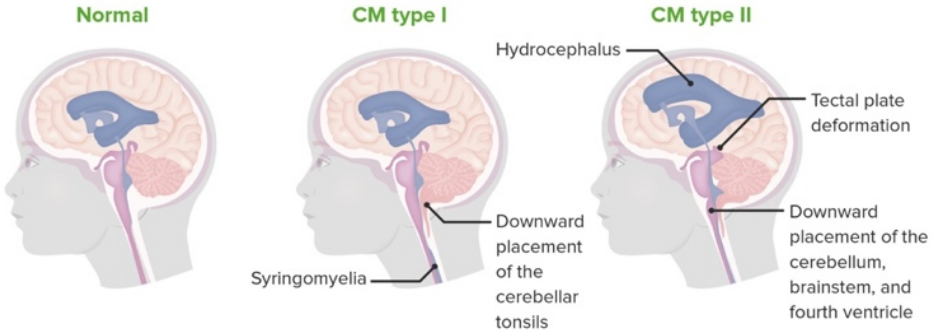


Figure 1. Chiari type I and II. Comparison between Chiari I and Chiari II malformations and normal morphology. Extracted from (3).

There are other types of Chiari which have been poorly described by some authors; such as Chiari 0, Chiari 1.5 or Chiari V (2).

- **Chiari 0 malformation**: patients who have a significant syrinx and small posterior fossa but no cerebellum tonsillar descent.
- **Chiari 1.5 malformation:** it is considered a progression of CIM, as there is the existence of cerebellar tonsillar herniation and also caudal herniation of some portion of brainstem (usually the obex of medulla oblongata) through the foramen magnum (4).
- **Chiari V malformation:** is poorly described, and it refers to the absence of the cerebellum, which leads to herniation of the occipital lobe through the foramen magnum.

Chiari 0	Chiari I	Chiari 1.5

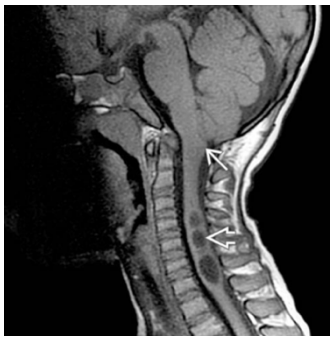
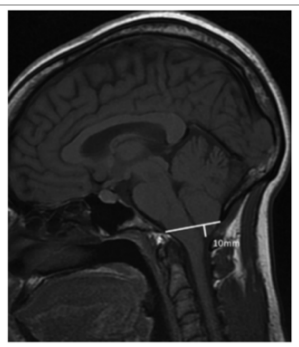
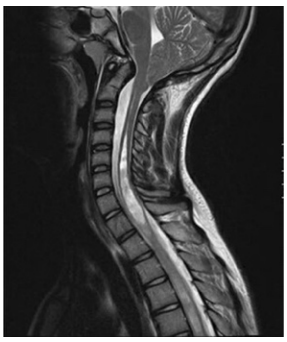
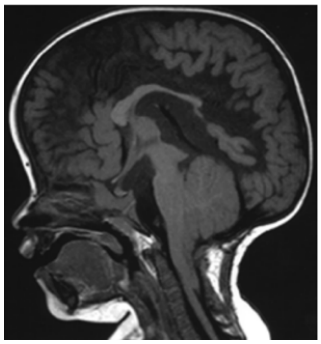
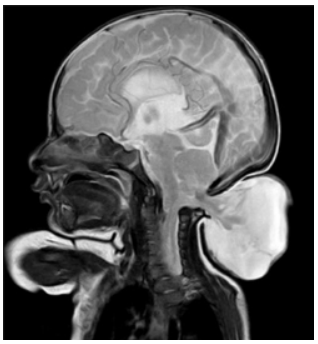
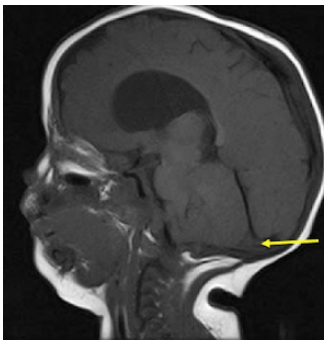

		

Figure 2. Chiari 0. Existence of hydrosyringomyelia with no cerebellar tonsillar ectopia in MRI, consisting of Chiari Malformation 0. Extracted from (5).	**Figure 3. Chiari I.** Descent of cerebellar tonsills more than 5mm below the foramen magnum (in this case, it is >10mm), demonstrated in MRI, resulting in Chiari II malformation. Extracted from (6).	**Figure 4. Chiari 1.5.** Image consisting of Chiari 1.5, which has the cerebellar tonsils descent combined with smaller posterior fossa and caudal migration of medulla oblongata. Extracted from (4).
Chiari II	**Chiari III**	**Chiari IV**
		
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1.1.3. EPIDEMIOLOGY

As it has been mentioned above, the most common type is CIM, which affects approximately 0.5 to 3.5% of the general population, with a slight female predominance (1.3 : 1) (1,10). It can be diagnosed in both children and adults, even though there is a study which identifies more cases in children and young adults rather than in older adults or elderly (11). It happens in 1 in 1,000 live births (10).

Moreover, there are many patients in which ACS is diagnosed incidentally while undergoing diagnostic imaging for other causes. This means that in the majority of cases, CIM is asymptomatic rather than symptomatic (1). The most common symptom in CIM is headache, in which prevalence is believed to be around 81% of the patients at presentation. However, it is important to consider that not all headaches can be directly attributable to the diagnosis (6).

Referring to the other types of Chiari, which are really rare, it is known that CIIM happens in 0.44/1000 births, with no predominant gender, in children with myelomeningocele. This type of Chiari has a decreased incidence thanks to prenatal folate supplementation, which in many cases prevents the appearance of malformations in the fetus. Unfortunately, CIIM associated to myelomeningocele has a high rate of mortality, especially in symptomatic patients within the first year of life (12).

Finally, Chiari III represents a 1-4.5% of all Chiari malformations, and along with the other types mentioned above, it is a rare form (1).

1.1.4. ETIOLOGY

The etiology of Chiari malformation is still unknown and debated, as there is not a single definitive cause. However, there are several theories which include the reduction of posterior fossa volume and the formation of myelomeningocele during pregnancy which could explain the majority of cases of CIM and CIIM, respectively (1).

Firstly, what happens in CIM could be explained by the reduction of posterior fossa volume. This occurs due to an inadequate development of skull bones which is insufficient to contain the entire cerebellum. Consequently, it causes the displacement

of cerebellum tonsils of >5mm through the foramen magnum. There are primary causes, such as a congenital posterior fossa hypoplasia, which can happen with mutations on chromosomes 1 and 22, and secondary causes; such as premature closure of sutures, calvarial dysplasia or genetic/syndromic alterations (1).

Secondly, myelomeningocele is an open neural tube defect which leads to an incomplete columnar bone formation. It consists of a protrusion of spinal cord and meninges, which can be seen from the patient's back, most frequently in the dorsal lumbar region (50% of cases). This is the main cause of Chiari II and III malformations and the suspected cause can be the folate deficiency or methylenetetrahydrofolate reductase mutations, which can increase the risk of neural tube defects. Consequently, this protrusion results in a lack of distension of the fourth ventricle due to leakage or redirected flow of CSF, causing its obstruction and consequently, a smaller posterior fossa and a cerebellar tonsillar herniation (1).

1.1.5. PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

The pathophysiology of this entity relies on the obstruction of the CSF, a transparent liquid in the central nervous system (CNS) which circulates in the ventricular system and the subarachnoid intracranial and intraspinal spaces. It is mostly produced by the choroid plexus in the lateral ventricle, since there it follows its circulation through the foramen of Monroe into the third ventricle and continues through the cerebral aqueduct (Sylvian aqueduct) into the fourth ventricle. Finally, it enters to the subarachnoidal space through the median and lateral foramens (named Luschka and Magendie foramens). A small volume of CSF passes through foramen magnum and ends in the ependymal canal of the spinal cord.

The foramen magnum is a bone structure located behind the medulla oblongata and under the cerebellum and connects the enchepalum with the spinal cord. Finally, CSF is principally absorbed from the arachnoid granulations in the superior sagittal sinus (13).

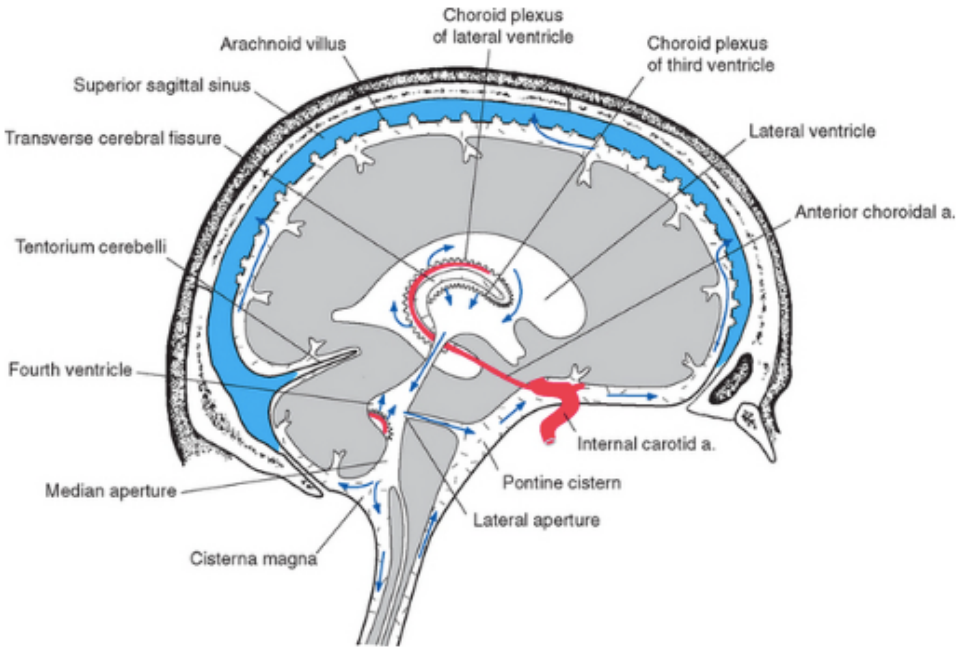


Figure 8. CSF circulation. CSF circulates in the ventricular system and in the subarachnoidal space. Extracted from (14).

The neurological signs and symptoms of Chiari malformations can be explained by the direct compression of neurological structures against foramen magnum and spinal canal and also due to the formation of cavitations filled with CSF within the spinal cord or brainstem. This last alteration, which is known as syringomyelia or syringobulbia, is caused by the obstruction and alteration of the CSF. Furthermore, as the cavity expands, neurological alterations become clinically significant (1).

The majority of patients with CIM are asymptomatic and when symptoms are present, they typically do not appear until adolescence or early adulthood (15).

One of the major issues on Chiari malformation management is the fact that there is a general and unspecific clinical presentation, which means that there is not a pathognomonic sign or symptom which definitely leads to diagnose these patients. Furthermore, the symptomatology can vary from mild to a more severe presentation and also depending on the pathological mechanism (see in **figure 9**) or even be asymptomatic and diagnosed incidentally in rutinary explorations (2).

CSF Obstruction	Compression of Brainstem, Cerebellum, or Cranial Nerves	Spinal Cord Dysfunction (syringomyelia)
Valsalva- or strain-induced occipital/upper cervical pain/headache	Swallowing difficulty/choking/aspiration, dysphagia	Upper motor neuron signs
Hydrocephalus	Hoarseness/dysarthria	Lower motor neuron signs
	Absent gag reflex	Pain and temperature sensory loss
	Central sleep apnea/snoring	Spasticity
	Downbeat nystagmus	Scoliosis (primarily thoracic levoscoliosis)
	Truncal ataxia	Motor weakness
	Tinnitus	
	Vertigo/dizziness	
	Autonomic symptoms (syncope, drop attacks, sinus bradycardia)	
	Trigeminal/glossopharyngeal neuralgia	
	Trigeminal sensory loss	
	Tongue weakness/deviation	
	Palatal weakness	

Figure 9. Symptomatology of Chiari malformation. Extracted from (2).

As it is shown in the table above, there are symptoms which can be associated to a concrete pathological alteration.

HEADACHE IN CHIARI I MALFORMATION

Firstly, CSF obstruction leads to the most common symptom in CIM, which is headache. However, consensus has not been reach as to how CSF flow obstruction can lead to headache (16).

Prevalence of any type of headache in CIM is around 81%, in where **transient cough-associated headache** (Valsalva +) is the most distinctive, seen in 30% of the patients with CIM (17). In these patients, the pain is typically localised in the suboccipital and/or in the upper cervical area and worsens with Valsalva manoeuvres (such as coughing, sneezing, and laughing). Additionally, are typically short-lasting (it only lasts seconds to less than 5 minutes) (6). The International Headache Society (IHS) established some criteria of Headache attributed to CIM, which helps in the clinical approach of the patient, together with the findings in MRI (see **Annex 1**).

Some authors explain that cough-associated headache happens due to a pressure dissociation between the head and spine. Firstly, there is an elevation of spinal pressure during coughing, displacing CSF to the head. Immediately after that, the displaced CSF returns normally in a healthy patient, but not in a patient with CIM due to the impaction

of cerebellar tonsils. Therefore, elevated spinal CSF pressure is associated with significant foramen magnum obstruction to CSF flow, which increases intracranial pressure and results in headache (16).

Cough-associated headache is the name given to the activity-associated headache mentioned above, which is characteristic of CIM. These type of headaches represent 1% of the clinical practice and can be primary or secondary, depending on the existence of an attributable cause (16):

- **Primary cough-associated headache**: those not attributable to another disorder. It is seen more frequently in older people (>60 years) and have a slight male predominance. It is short-lasting (seconds to minutes or up to 2 hours) and has a bilateral posterior character. It also responds well to treatment with pain medication (6).
- **Secondary cough-associated headache** (for e.g. due to CIM): it is more frequent in younger people (<40 years) and has a female predominance. Although it is tipically a suboccipital pain, there are other variants. For example, a patient could have a brief cough-associated headache on the frontal area (6).

Table 1. Primary and secondary cough-associated headaches. Adapted from (6).

Primary cough-associated headache	Secondary cough-associated headache
Less frequent in CIM patients	More frequent in CIM patients
Older people (>60 years)	Younger people (<40 years)
Slight male predominance	Slight female predominance
Bilateral occipital pain	Suboccipital pain principally
Lasts from seconds to minutes or even up to 2 hours	Lasts from seconds to 5 minutes
Respond to conventional pain treatment	Respond to CIM successful treatment.

Although there is a characteristic headache on patients with CIM, it is not the most frequent. In 70% of the cases, patients clinically are presented with **atypical types of headache,** such as migraine, tension-type or any other from the cluster variety (6).

Some authors inform that patients who only presented with atypical headache and underwent surgery, **50%** had an improvement in their headaches, whereas patients with typical CIM headache improved in the 80% of the cases (18,19).

Due to the high prevalence of these primary headaches, it is challenging to distinguish between headaches which are related to CIM and those that coexist in a fortuitous and independent way with CIM (20).

Migraine is common among Chiari patients, which refers to a severe type of headache which usually recur and can lead to changes in vision known as aura. As it is a common type of headache, it is treated with a specific analgesic treatment, but sometimes it masks the Chiari problem and delay its accurate diagnostic and treatment (21). Some authors described notable differences that were statistically significant observed in two groups of patients: Chiari group with migraine and general migraine group (21):

Table 2. Migraine in Chiari group and control group. Adapted from (21).

Chiari group with migraine	General migraine group
Migraines in a younger age (13 years)	Migraines in an older age (25 years)
Suffered from migraine 6 days more a month	Suffered from migraine 6 days less a month
Higher intensity (7/10)	Lower intensity (5/10)
More nausea and vomiting	Less nausea and vomiting

Tension-type like headache have also been described to be associated with CIM. It is often described as a feeling like a tight band around the head causing mild-to-moderate pain. Moreover, cluster type headache can also be found in these patients, a unilateral and extremely severe headache with autonomic features and circadian periodicity. It is less commonly related to CIM.

The wide variety of headache types that can be present in patients with CIM makes it more difficult for neurosurgeons to make a surgical decision. In fact, there are authors who have described different types of headache presented in CIM patients, including both typical and atypical headaches (see **table 3**) (6).

Table 3. **Types of headache in CIM.** Adapted from (6).

TYPES OF HEADACHE	HEADACHE CHARACTERISTICS
Type 1	Transient localized suboccipital cough-related headaches (triggered by cough, Valsalva, sneezing, exercise, bending forward or laughing).
Type 2	Transient localized non-occipital or generalized cough-related headaches.
Type 3	Constant localized (occipital or non-occipital) or generalized headache (constant daily headache) that may be exacerbated by cough.
Type 4	Transient or constant suboccipital headaches that are not cough-related.
Type 5	Transient or constant localised non-occipital or generalized headaches that are not cough related.

OTHER SYMPTOMATOLOGY

Another finding that also results from the CSF obstruction is hydrocephalus, which is produced by the accumulation of extracellular fluid and consequently, an increase in CNS pressure (22). This happens most frequently in CIIM.

Other unspecific symptoms include: ocular disturbances, otoneurologic symptoms (dizziness, hearing loss, etc), truncal ataxia and generalized fatigue, scoliosis in the pediatric population, … (see more in **figure 9**).

Furthermore, in patients with syringomyelia, myelopathy is clinically presented as a dissociated sensory loss (loss of pain and temperature sensation and preserved fine touch and proprioception) and motor weakness.

In the neurological exploration of the patient, first and second motoneuron signs can also be present. Moreover, other signs may be evaluated, such as cerebellar signs, which include ataxia, dysmetria, nystagmus and lower cranial nerve deficits (IX, X, XI, XII) which lead from direct compression of the cerebellum or medulla at the foramen magnum or from syringomyelia or syringobulbia (1).

1.1.6. DIAGNOSIS AND EVALUATION

MAGNETIC RESONANCE IMAGING

Diagnosis of ACS is made with clinical findings, which can be really unspecific, and confirmed by **MRI,** which is the test of choice when it comes diagnose and evaluate Chiari malformation, especially Chiari I.

When diagnosing CIM, a brain and spinal MRI are useful to demonstrate cerebellar tonsillar descent greater than 5mm below the foramen magnum. It is important to note that the extension of tonsillar ectopia does not correlate with the severity of symptoms (1,2).

Other findings on MRI can be the presence of a spinal syrinx and also a decreased size of the posterior fossa. Cranial imaging is also performed in order to discard other causes which could cause tonsillar displacement, such as hydrocephalus and mass lesions.

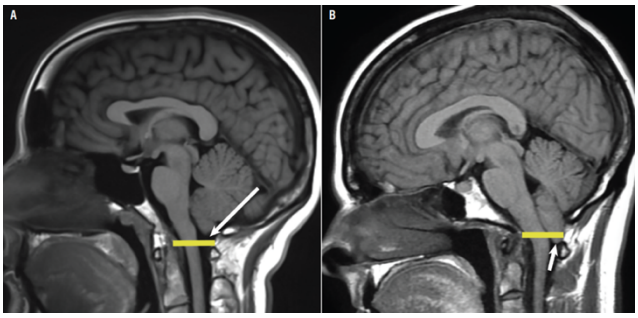


Figure 10. MRI showing Chiari malformation. A normal MRI in the left; and MRI demonstrating a tonsillar ectopia >5mm below the foramen magnum, representing a patient with CIM in the right. Extracted from (23).

Once it has been performed the MRI and demonstrated the presence of the malformation, a holospinal study, which includes thoracic and lumbar spine MRI, is made in order to detect if there are other complications associated.

CINE-FLOW MRI

CSF circulates around and out the skull and down toward the spine in every heartbeat, in response to the flow of the blood entering the brain. Cine-flow MRI is a type of MRI sequence which is taken in the same way as a conventional MRI but with the addition of monitoring the heart rate in order to analyse CSF flow. Therefore, it is useful in the diagnosis of CIM to determine if there are CSF flow alterations at different points in the cardiac cycle, which sometimes leads to the formation of syrinx. (1,2).

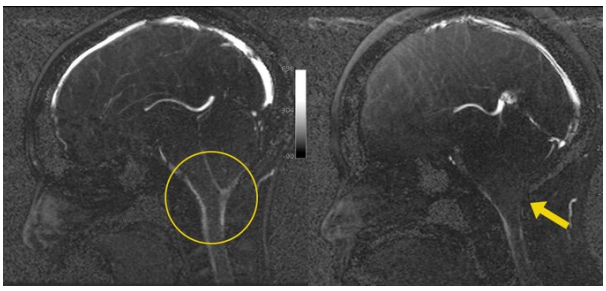


Figure 11. Cine-flow MRI. A normal flow cine MRI in the left and blocked CSF flow in the right. Extracted from (24).

NEUROPHYSIOLOGICAL ASSESSMENT

Although MRI is the diagnostic test for Chiari, there are other tests which are performed and are useful to assess the severity of the compression on the brainstem, such as functional neurophysiological studies (1,2):

- **Cerebral stem auditory evoked potentials:** to assess the degree of alterations in the auditory pathway at the level of the protuberance.
- **Somatosensory evoked potentials:** to study the functionality of the ascending sensory pathway from the peripheral nerve to the parietal cortex. It detects whether if there is a delay in the conduction of the nerve impulse and at what level.
- **Nocturnal polysomnography:** evaluation of the low cranial pairs (mainly IX and X). The compression of this nerves at the level of the bulb can cause obstructive apneas during sleep.

OTHER TESTS

When MRI is not available or cannot be used, myelography is performed. Furthermore, patients undergo a computed tomography (CT) scan and laboratory tests which are useful for surgical planning (1).

An ultrasound in utero is often used to make the first evaluation for the other types of Chiari (II-IV). This is usually performed in the second-trimester and enables the diagnosis by featuring typical imaging which would indicate some alterations such as: banana sign (classic sign of Chiari II and also distal neural tube defect), the presence of meningoencephalocele, and others (1).

Fetal MRI can also show some signs of Chiari malformation, especially type IV and V, such as hypoplasia/aplasia of cerebellum (1).

1.1.7. TREATMENT/MANAGEMENT

The management of these patients can be medical or surgical (1).The choice is basically decided depending on the symptomatology of the patient and also of MRI and cine-MRI findings. Proper selection of patients for surgery is important in order to avoid undergoing a surgery which can result in unexpected outcomes and possible complications.

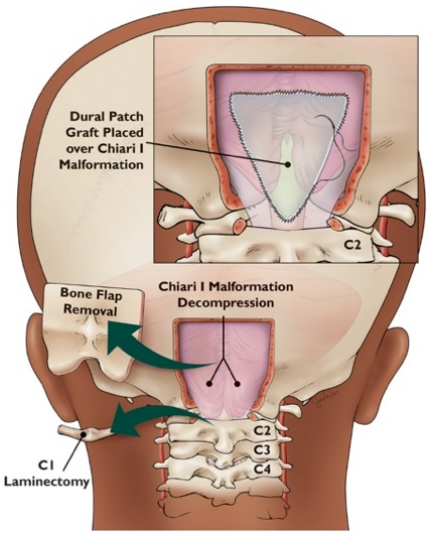
It is important to highlight that in CIM, most of the patients remain asymptomatic, even if they also present syringomyelia. In these patients, surgical option is usually not observed. Instead, they will be monitored periodically with MRI studies and treated adequately when symptomatology appears (1).

Initially, symptomatic patients can be managed medically: headache and neck pain can be treated with muscle relaxants; non-steroidal anti-inflammatory drugs (NSAIDs), and temporary use of cervical collar. If these symptoms worsen, surgical option should be considered (1).

The chosen surgical standard method is usually the posterior fossa decompression (PFD), which its main objective is to decrease pressure of the cerebellum and hindbrain and also to re-establish the CSF circulation (18). Still, it is unknown the benefits of this surgical intervention; there are patients who do not show clinical improvement post-surgery, especially those with an atypical headache. Furthermore, decompression is contraindicated when there is a tonsillar herniation due to another pathology, for example, when is due to intracranial hypotension or the presence of a mass (1).

In order to make the PFD, it is needed a suboccipital craniectomy, often associated with C1 and/or C2 laminectomy, depending on the extension of cerebellar tonsillar migration. Therefore, the incision usually goes from below the external occipital protuberance to the spinous process of C2 (2).

Once the decompression has been made, sometimes it is made a dural opening and dissection of arachnoid adhesions if present (depending on the decision of the surgeon, who contrast risks vs benefits). The dura is often opened in a Y-shaped way to allow sufficient decompression and followed by a duraplasty if needed (1,2).



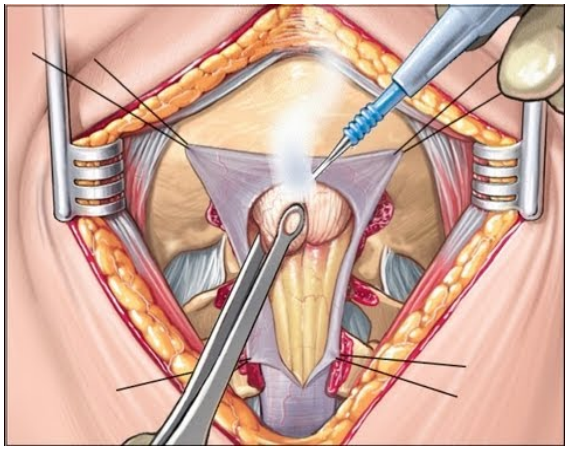


Figure 12 (left). **Posterior fossa decompression.** Representation of PFD in CIM, showing the bone removal, C1 laminectomy, and after that the collocation of dural patch. Extracted from (25).

Figure 13 (right). **Opening of the dura.** Representation of PFD in CIM, showing the Y-shaped way to open the dura. Extracted from (25).

1.1.8. COMPLICATIONS OF POSTERIOR FOSSA DECOMPRESSION

Surgical intervention in Chiari sometimes do not seem to improve clinical presentation post-surgery and some authors believe that it is because there are some microstructural alterations in white matter which are irreversible (26).

Therefore, it is discussed if it is worth taking the risk and operate the malformation or instead, offer conservative treatment and follow a radiological control in order to observe if there is a symptomatology progression and of other neurologic signs or formation of syrinx.

Usually after the surgical intervention, patients refer headache, neck pain, dizziness... which are common expected symptoms in a normal immediate post-surgical evolution and therefore are not considered as complications.

However, all surgical procedure can lead to complications, and PFD is one of them (see **Annex 2** in "risks and complications"). Dubey et al. studied the complications of PFD surgery and observed that the most frequent complication encountered was CSF leakage (13%), meningitis (9.2%), wound infection (7%), central nervous paralysis (4.8%), cerebellar edema (5%), hydrocephalus (4.6%), cerebellar hematoma (3%), cerebellar mutism (1.2%) and death (2.6%) (27).

1.1.9. POSTOPERATIVE OUTCOMES

Chicago Chiari Outcome Scale (CCOS) is a scale used to evaluate postoperative improvement of patients with Chiari malformation. This evaluates 4 postoperative outcomes (28).

- **Pain symptoms** (e.g. tussive headache, neck and shoulder pain)
- **Non-pain symptoms** (e.g. ataxia, vertigo, tinnitus, paresthesias)
- **Functionality** (ability to attend to school/work/daily activities…)
- **Surgical complications** (from the time of surgical descompression to the last clinic visit).

These parameters are subjectively punctuated from 1-4. The total score ranges from 4-16, in which a total of 4 represents an incapacitated outcome and 16 an excellent outcome (see **table 4**).

Table 4. The Chicago Chiari Outcome Scale. Adapted from (28).

PAIN	NON-PAIN	FUNCTIONALITY	COMPLICATIONS	TOTAL SCORE
1- Worse	**1-** Worse	**1-** Unable to attend	**1-** Persistent complication, poorly controlled	**4-** Incapacitated outcome
2- Unchanged and refractory to medication	**2-** Unchanged or improved but impaired	**2-** Moderate impairment (<50% attendance)	**2-** Persistent complication, well controlled	**8-** Impaired outcome
3- Improved or controlled medication	**3-** Improved and unimpaired	**3-** Mild impairment (>50% attendance)	**3-** Transient complication	**12-** Functional outcome
4- Resolved	**4-** Resolved	**4-** Fully functional	**4 -** Uncomplicated course	**16** - Excellent outcome

1.1.10. PROGNOSIS

There is a different prognosis for the four types of Chiari malformation. The most frequent type of Chiari, type I, has a good prognosis, especially when patients do not have neurologic deficits. Moreover, in Chiari II neonatal mortality is approximately around 3%. In other rare variants of Chiari, prognosis is not that good and early death occurs (1).

1.2. DIFUSSION TENSOR IMAGING

1.2.1. INTRODUCTION

Diffusion tensor imaging (DTI) is a relatively new MRI technique that uses anisotropic diffusion to estimate the axonal organization of the brain in white matter (WM) tracts (29). It is a non-invasive method that gives information about the direction and movement of water molecules *in vivo*, and therefore enables to study white matter tracts and the connectivity of different brain regions, which is information that conventional MRI does not provide (30,31). Thus, DTI is useful to determine the relationship between the abnormalities in the integrity of white matter pathways and neurological defects (32).

Molecular diffusion follows a Brownian motion, which refers to the irregular and random movement of small particles immersed in a fluid. The differences in the Brownian motion of water in the CNS is what generates the signal contrast of DTI.

There are 2 types of diffusion: **anisotropic**, when is oriented in one direction; and **isotropic,** when diffusion goes in all directions. In the encephalon, diffusion follows an anisotropic diffusion. This means it goes parallel to nerve fibers due to the presence of myelin, which restricts diffusion in a direction perpendicular to the fibers. This pattern is what enables DTI to track fibers pathways and to measure in a qualitative and quantitative way the microscopic integrity of white matter structures of congenital and acquired disorders of the brain (30).

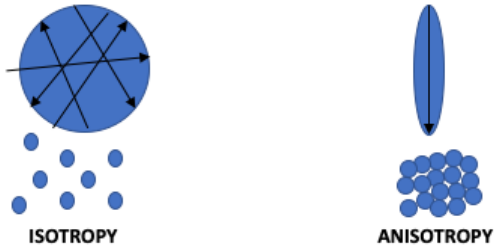


Figure 14. Isotropy and anisotropy. Representation of water direction molecules following an isotropic and anisotropic diffusion.

Fiber tractography (FT) is a 3D reconstruction technique to assess neural tracts using the data collected by DTI. The convention for colour coding is the following (29)**:**

- Superior to inferior direction or viceversa (projection fibers): coloured blue.
- Anterior to posterior or viceversa (association fibers): coloured green.
- Right to left or viceversa (commissural fibers): coloured red.

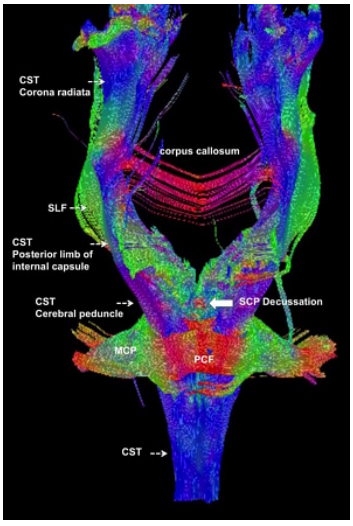


Figure 15 (left). Brain fiber tractography. FT in a normal subject showing the decussation of the superior cerebellar peduncle. Extracted from (29).

Figure 16 (right). **Spine fiber tractography**. FT of a patient with syringomyelia. The black arrow shows a fiber displacement in the centro-medullary cavity. Extracted from (33).

Furthermore, it has been demonstrated that DTI summarizes the clinical role in various diseases such as amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's dementia, epilepsy ischemic stroke, traumatic brain injury, spinal cord injury, and much others (34,35).

1.2.2. TENSOR

In diffusion studies, molecular movement is detected through a predetermined axis, which is fixed by the orientation of the gradient of an applied field. Diffusion tensor uses three eigenvectors (x, y and z) which are represented each one by three eigenvalues (λ1, λ2, λ3).

These values indicate the diffusion or displacement for each specific vector, and enables to quantify water diffusion in three orthogonal axes of the diffusion ellipsoid (35).

- x-vector: represented by Dxx, Dxy and Dxz
- y-vector: represented by Dyx, Dyy and Dyz
- z-vector: represented by Dzx, Dzy and Dzz.

$$\mathcal{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

There are in total 9 variables which can be arranged in a 3x3 metrics which is the mathematical representation of the tensor illustrated above (36).

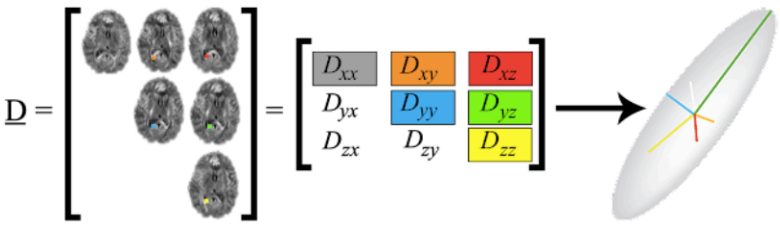


Figure 17. Diffusion image to tensor. Representation of 6 gradient direction. Extracted from (37).

1.2.4. PARAMETERS

The four parameters which provide the quantitative information obtained in DTI are the following, being the first and the second parameters the most relevant as they are markers of fiber tract integrity (29,31):

- **Fractional anisotropy (FA):** measures the degree of anisotropy of water molecules. It is the difference between the largest eigenvalue as compared to the others:

$$\sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_1-\lambda_3)^2+(\lambda_2-\lambda_3)^2}}{\sqrt{(\lambda_1^2+\lambda_2^2+\lambda_3^2)}} = \text{fractional anisotropy (FA)}$$

  FA values vary from 0 to 1, indicating:

  - **0:** infinite isotropy (equal movement in all directions). Ex: in CSF.
  - **1:** infinite anisotropy (maximum tissue organization). Ex: in fiber bundles.

  Although DTI assesses 4 parameters, FA is the best known for the evaluation of WM and its alteration is a very sensitive parameter in the assessment of WM pathology, as it serves as a marker of CNS axonal integrity (see in **figure 18**) (33).

  Initially, an external compression of the brain provokes an increase anisotropy (higher FA values) due to diffusion restriction in the direction perpendicular to the compression. However, when this process is cornified may cause an irreversible injury (edema, haemorrhage, axonal loss..) and an unrestricted diffusion of water molecules, resulting in the decrease in FA (38).

  Thus, FA is influenced by axonal microstructural integrity and there are brain regions in which there is a predominant directionality of fiber orientation pattern, such as in the corpus callosum (CC), in which FA is reliable (38).

- **Mean Diffusivity (MD) or Apparent Diffusivity Coefficient (ADC):** indicates the magnitude of water diffusion. It considers that there are barriers such as myelin which interfere with diffusion. For example, if there are more cellular membranes in the tissue, there will be less molecular diffusion and therefore,

lower ADC. Instead, when there are fewer barriers, there will be more diffusion and consequently, higher ADC. It quantifies the average of all three eigenvalues:

$$(\lambda_1 + \lambda_2 + \lambda_3)/3 = \text{mean diffusivity (MD)}$$

- **Axial Diffusivity (AD):** reflects axonal health by studying the parallel movement of diffusivity. It only quantifies the value of lambda 1:

$$\lambda_1 = \text{longitudinal (axial) diffusivity(AD)}$$

- **Radial Diffusivity (RD):** it indicates myelin sheath integrity by studying the perpendicular movement of diffusivity. It quantifies the average between lambda 2 and lambda 3:

$$(\lambda_2 + \lambda_3)/2 = \text{radial diffusivity (RD)}$$

Parameter	Function	Marker of	Increased	Decreased
Fractional anisotropy	Preferential diffusion directionality	Axonal integrity Fiber density Fiber coherence	Acute compression Decrease in axon diameter Axonal regeneration/plasticity Vasogenic edema Gliosis	Chronic compression Axonal injury/loss/degeneration Demyelination Dysmyelination
Mean diffusivity/apparent diffusion coefficient	Diffusion magnitude regardless of the direction	Myelin integrity Fiber density Fiber coherence	Chronic compression Vasogenic edema Demyelination Dysmyelination Axonal degeneration	Acute compression Cytotoxic edema High myelination
Axial diffusivity	Diffusion in the direction parallel to the white matter tracts	Axonal integrity Fiber density	High myelination High density of neurofilaments and microtubules Increase in axon diameter and density Gliosis Vasogenic edema	Axonal injury/loss Axonal degeneration (reduction of neurofilaments and microtubules) Decrease in axon diameter and density
Radial diffusivity	Diffusion in the direction perpendicular to the white matter tracts	Myelination Fiber density	Demyelination Dysmyelination Vasogenic edema Decrease in axon density	High myelination Increase in axon density

Figure 18. Characteristics of DTI parameters. Microstructural interpretation of DTI parameters within the white matter tracts. Extracted from (26).

1.2.5. CLINICAL APPLICATIONS

DTI is used for the assessment and early detection of some diseases and malformations and also for surgical planning. Some of the most common applications include (33,34):

- Detection of early disease in Alzheimer patients.
- Early identification of musculoskeletal and peripheral nerve pathology.
- Assessment of schizophrenia, focal cortical dysplasia, multiple sclerosis,

traumatic brain injury, diffuse axonal injury…

- Presurgical planning for brain and spine (specially lesions with mass effect, such as tumors).

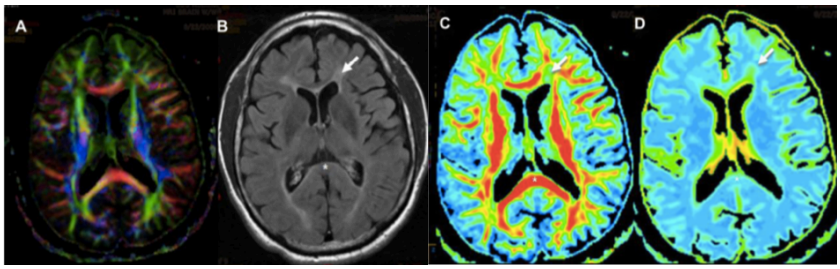


Figure 19. Findings of DTI in multiple sclerosis lesions. **A**. FA color-coded map**. B.** Fluid-attenuated inversion recovery (FLAIR). **C.** FA map**. D.** MD map (39).

1.2.6. CONTRAINDICATIONS

Contraindications of DTI are the same as MRI. The main serious complication with MRI is the interaction of the magnetic field with implanted devices and ferromagnetic objects of patients (40). There are situations in which DTI should preferably not be performed or situations in which safety should be assessed individually in each case:

Cardiac pacemaker and implanted defibrillator	Swan-Ganz catheter
Internal pacing wires	Bullets near vessels or vital organs
Metallic foreign body in the eye	Cerebral aneurysm clips
Deep brain stimulator	Magnetic dental implants
	Pregnancy (generally avoided, especially during the 1st trimester)

Other potential contraindications are claustrophobia (requires sedation), having tattoos and cosmetics, pregnancy and postpartum, and others (41).

1.2.7. DIFFUSION TENSOR IMAGING IN CHIARI I MALFORMATION

Lately, DTI has been used in patients with Chiari malformation in order to study white matter tract dysfunction. Some of these studies have been described in a systematic review: 3 studies evaluated the correlation between DTI changes and the symptomatic

appearance; 2 studies compared DTI findings between patients with and without syringomyelia and other 3 studies assessed DTI changes and response to PFD.

Several conclusions were that DTI could serve as a reliable predictor of postoperative outcomes and therefore, facilitate an appropriate selection of surgical candidates (26).

Antkowiak et al. note that there is no reliable diagnostic tool to measure brainstem compression severity and underlying microstructural alterations. They also outline the fact that studying parameters in DTI can help clinicians to assess the extent and character of neural structure damage (26).

Houston et al. associated the DTI abnormalities in patients with CIM with self-reported pain compared with healthy controls (42). Conclusions were that greater FA and lower MD in several brain regions including the internal capsule, corpus callosum, longitudinal fasciculi and corona radiata were found to be related to the self-reported pain and headache that patients specified they had.

Kumar et al. described the correlation between DTI metrics and neurocognitive abnormalities in patients with CIM. These reported that decreased FA in genu, splenium and fornix, and increased RD in cingulum were correlated with worse neuropsychological test results. Conclusions they made were that DTI could serve as an objective measure of microstructural alterations which reflect patient's clinical status and express the severity of the cognitive decline (32).

Kurtcan et al. also evaluated differences between DTI parameters obtained from patients with CIM and borderline tonsillar ectopia and also to determine the correlation between DTI metrics and the severity of tonsillar ectopia (43). Also described that FA values at the medulla oblongata level in patients with CIM are higher than in controls (43).

Furthermore, Krishna et al. stated that neurological dysfunction in CIM results from brainstem compression, and therefore, studying FA values in the brainstem resulted to normalize after PFD. Authors in this study also suggested that higher FA levels in CIM are due to an increase in inflammatory compression (38).

2. JUSTIFICATION

Arnold Chiari syndrome is one of the many malformations which mainly neurologists and neurosurgeons come across in their consultations, specially Chiari I malformation (CIM). It represents only 0.5-3.5% of the general population (1,10), but even so, its clinical management is not completely clear as the majority of patients remain asymptomatic or with a very non-specific and non-pathognomonic symptomatology. Additionally, there are no specific surgical guides and sometimes it is difficult to explain the lack of postoperative clinical improvement (26). Therefore, the management of the patients with CIM is generally debated within the professionals, especially of those who clinically presenting with atypical headache (some authors describe only a 50% of headache improvement post-surgery in these patients (18)).

Posterior fossa decompression (PFD) is not a very complex surgery but still it is made in a delicate anatomic area and can lead to complications (see ***1.1.8***.). All surgeries have its risks and benefits which must always be assessed and personalised in each case, with the objective that patients achieve a post-surgical clinical improvement.

Lately there have been studies associating the use of DTI and CIM. For example, Krishna et al. observed patients who showed a decrease in their brainstem fractional anisotropy (FA) values after surgery. Authors affirmed that this was due to the increasing space in the posterior fossa and the alleviation of pressure on the spinal cord after PFD (38). Kurtcan et al. also describe that FA values at the medulla oblongata level in patients with CIM are higher than in controls (43).

At date there are no prognostic tools for surgical outcome in CIM patients with atypical headache, and therefore postoperative outcomes cannot be reliably predicted (26). Hence, this study pretends to demonstrate whether if measuring brainstem FA values in these patients could be a strong predictive tool (with a sensitivity >90%) to select those who will improve. Thus, a prognostic accuracy study is proposed.

3. HYPOTHESIS

3.1. RESEARCH HYPOTHESIS

Higher brainstem fractional anisotropy values in patients with Chiari I malformation presenting an atypical headache have a high sensitivity (S>90%) in estimating good surgical outcome.

3.2. NULL HYPOTHESIS

Higher brainstem fractional anisotropy values in patients with Chiari I malformation presenting an atypical headache does not have a high sensitivity (S>90%) in estimating good surgical outcome.

4. OBJECTIVES

4.1. MAIN OBJECTIVE

The main objective is to evaluate the sensitivity of having higher brainstem fractional anisotropy values as a predictor of good surgical outcomes in patients with CIM clinically presenting with an atypical headache.

In order to choose the most appropriate cut-off fractional anisotropy value to discriminate higher values from lower ones (with the highest specificity and sensitivity), a ROC curve analysis will be made.

4.2. SECONDARY OBJECTIVES

- To measure the following parameters in order to analyse in a more accurate way the validity of using brainstem FA parameters:
  - Specificity.
  - Negative predictive value (NPV) and positive predictive value (PPV).
  - Likelihood ratio (LR)
  - Diagnostic efficiency (DE).
- To evaluate if headache pain improves after surgery using the visual analogue scale (VAS) (see in **Annex 3**).
- To compare changes in postoperative brainstem FA values from preoperative ones and evaluate its association with headache improvement or not.
- To compare the results between the following groups to see if there are statistically significant changes:
  - According to age: younger (18-35 years) / older (>35 years)
  - According to sex: male / female
  - According to pre-surgical VAS score: higher score / lower score

5. METHODOLOGY

5.1. STUDY DESIGN AND SETTING

This research is designed as a non-experimental longitudinal study in order to determine the accuracy of brainstem FA values in predicting surgical outcomes in patients with CIM with an atypical headache.

The study will have a duration of approximately 2 years and will be conducted in the neurosurgery department of three hospitals: Hospital Universitari Josep Trueta (HUJT) in Girona, Hospital Universitari Germans Trias i Pujol (HUGTiP) in Badalona and Hospital Universitari Arnau de Vilanova (HUAdV) in Lleida.

5.2. STUDY POPULATION

The study population will include all patients over 18 years old diagnosed with CIM who clinically presents with an atypical headache in HUJT, HUGTiP and HUAdV. These patients will be offered to participate and given a written informed consent in case they want to take part of this research.

5.2.1. INCLUSION CRITERIA

- Patients with CIM clinically presenting with an atypical headache (which does not meet criterion C of the table shown in **Annex 1**).
- Patients over 18 years old.
- Patients who have signed consent form after being informed about the risks and benefits of the study and also of the surgical procedure.

5.2.2. EXCLUSION CRITERIA

- Asymptomatic patients with CIM.
- Patients with CIM presenting:
    - Valsalva-induced headache (typical headache)
    - The existence of spinal syrinx, hydrocephalus, syringohydromyelia.
    - Severe neurological deficits attributable to CIM

- Patients under 18 years-old with CIM.
- Patients with CIM who have a contraindication to PFD: when tonsillar herniation is due to another pathology, for example, when is due to intracranial hypotension or the presence of a mass (1).
- Patients with CIM who have a contraindication to DTI (see in ***1.2.6***).
- Patients presenting with secondary headache disorders such as idiopathic intracranial hypertension or with intracranial abnormalities (e.g. subdural haematoma, tumor or abscess).

5.2.3. WITHDRAWAL CRITERIA

- Patients with DTI images which have a significant motion artefact or missing or incomplete image sets.
- Patients who will be lost during the follow-up of the study due to uncontrollable reasons.
- Patients who passes away during the duration of the study.
- Patients who undergo unexpected complications during the surgery in which the surgeon has the obligation to change the surgical technique stipulated.

5.3. SAMPLE

5.3.1. SAMPLE COLLECTION

Sample recruitment will be performed with a consecutive non-probabilistic sampling method. All patients diagnosed with CIM who meet the inclusion criteria and none of the exclusion ones proposed in the study will be requested to participate. They will be recruited while undergoing presurgical consultation in HUJT, HUGTiP and HUAdV with an estimated time of 1 year.

Moreover, patients will be informed about the purpose of the study and will be given the information sheet and consent form (see **Annex 4 and 5**). It is important to highlight to the patients the voluntarily and confidential aspects of their participation, as well as their right to withdrawal from the study at any time.

Once the informed consent has been signed, the participant will be given a new appointment with the neurosurgeon in order to complete the Data Collection Sheet (see **Annex 6**).

5.3.2. SAMPLE SIZE

In this study we used the program *Calculadora de Grandària Mostral (*GRANMO) to calculate the sample size of our study:

As a preliminary study, we calculated with a confidence level of 95% and a precision of approximately 10% percentage units, that the random sample of **39 individuals** is sufficient to estimate a sensitivity >90% of higher brainstem FA values in predicting good surgical outcome in our study population. In order to calculate this sample, we have also considered the estimated drop-out rate of 10% (which includes patients who meet withdrawal criteria).

5.4. VARIABLES AND MEASUREMENTS METHODS

5.4.1. STUDY VARIABLES

Our study variables are:

- **Brainstem FA parameters in DTI:** in order to evaluate the accuracy of FA values in predicting a good surgical outcome, the study will focus on a specific region of interest (ROI), which is the brainstem, specifically in the medulla oblongata. The cut-off FA value to differentiate lower and higher values in this region will be measured from a ROC curve analysis, with the higher sensitivity and specificity. Therefore, according to the cut-off found, FA values of brainstem will be analysed and categorised as a continuous quantitative variable:
    - **Lower FA values**
    - **Higher FA values**
- **Surgical outcome:** it will be evaluated with the comparation between post-surgical and pre-surgical VAS score of every participant (see scale in **Annex 3**). This scale measures pain symptoms in a scale from 0 to 100mm.

Patients will be assessed firstly at the start of the study (pre-surgical VAS) and then in the follow-up visit after surgery (post-surgical VAS) and classified into 2 outcome groups:

- **Unsatisfactory surgical outcome:** if there is no improvement of >20mm in post-surgical VAS score compared to pre-surgical VAS score.
- **Good surgical outcome:** if there is an improvement of ≥20mm in post-surgical VAS score compared to pre-surgical VAS score.

5.4.2. COVARIATES

- **Sex:** it will be considered as a qualitative dichotomous variable: male or female. The answer will be extracted from ID card or any other official document and collected into the Data Collection Sheet (see in **Annex 6**).
- **Age:** it will be considered as a continuous quantitative variable measured in years. The answer will be extracted from ID card or any other official document and collected into the Data Collection Sheet (see in **Annex 6**).
- **Ethnicity:** it will be considered a qualitative nominal variable according to 5 categories, which will be (I) African, (II) Asian, (III) Caucasian, (IV) Latin-American and (V) others. It will be collected into the Data Collection Sheet (see in **Annex 6**).
- **Medical history potentially related to headache:** it will be considered as a dichotomic nominal qualitative variable: yes/no. If the answer is "yes", the person will have to respond a number of options we will consider in the Data Collection Sheet (see in **Annex 6**).
- **Headache onset:** it will be considered as a continuous quantitative variable measured in years/months. It will be extracted from Data Collection Sheet (see in **Annex 6**).
- **Tonsillar ectopia:** it will be considered as a continuous quantitative variable measured in mm. It will be extracted from MRI results at the moment of CIM diagnosis.

Table 5: The study variables and covariates table.

MAIN VARIABLES			
Variables	**Type of data**	**Categories or value**	**Measure instrument**
Alterations in DTI	Dichotomic quantitative	a. Higher brainstem FA values b. Lower brainstem FA values	DTI
Surgical outcome	Dichotomic qualitative	a. Good surgical outcome b. Unsatisfactory surgical outcome	VAS
COVARIATES			
Sex	Dichotomic qualitative	a. Male b. Female	Data collection sheet (DCS)
Age	Continuous quantitative	Number of years (>18)	DCS
Ethnicity	Nominal qualitative	a. African b. Asian c. Caucasian d. Latin-American e. Others	DCS
Medical history potentially related to headache	Nominal dichotomous qualitative	a. Yes b. No	DCS
Headache onset	Continuous quantitative	a. >3 months b. <3 months	DCS
Tonsillar ectopia	Continuous quantitative	a. 5-10mm b. >10mm	MRI

5.5. MEASUREMENT TOOLS

5.5.1. IMAGING TECHNIQUE

An MRI 1.5-T will be used in our study in order to acquire DTI sequence analysis. All DTI data sets will be reviewed by 2 radiologists from HUJT simultaneously using commercial image viewing software and will be inspected visually for motion so that there are no severe motion artefacts detected.

The DTI protocol will consist of a single-shot spin-echo echo-planar sequence with TR/TE, 4094/89 ms; matrix, 112x110; field of view (FOV), 125 x 2.24 mm^2; slice thickness, 20mm; interslice gap, 1.5 mm; number of slices, 50; spatial resolution, 1.54. Thirty different diffusion gradient directions will be used with b = 800 s/mm^2, and another image with no diffusion gradient will be obtained (b = 0 s/mm^2). The DTI parameters will be calculated, specifically, FA values.

In this study, the region of interest (ROI) will be the brainstem, concretely in medulla oblongata. Size adaptation and placement of all ROI will be performed by the 2 experienced radiologists, and will be drawn with maximum care and with the same size in all patients.

DTI will be used twice during the study: firstly, when patients are diagnosed with CIM and accept to participate in the study, and then at the end of the study during the follow-up visit. Brainstem FA parameters will be measured in both DTI procedures.

5.5.2. VISUAL ANALOGUE SCALE

The VAS score is widely used to measure pain intensity after surgery (44). Patients will be asked to mark their level of pain in the 100mm line of the VAS score at two different phases of the study: pre-surgical and post-surgical. It is an horizontal line going from 0mm “No pain” to 100mm “Maximum pain”.

This will be the tool which will help us to evaluate the surgical outcome in patients with CIM and atypical headache.

It includes 5 categories of severity of pain (see **Annex 3**):

1. **Very low or low pain**: values between 0-20mm.
2. **Mild pain:** values from 20-40mm.
3. **Moderate pain:** values from 40-60mm.
4. **High pain:** values from 60-80mm.
5. **Very high pain:** values from 80-100mm.

A clinically significant improvement is considered when there is a decrease of **≥20mm** in postoperative VAS score compared to preoperative VAS score.

5.6. DATA COLLECTION

All data collected during the study will be saved in the clinical history of the patient, in the SAP system and in the Research Electronic Data Capture (REDCap), which is a secure platform database. Covariables and other data collected during the study will also be filled in the Data Collection Sheet (see in **Annex 6**).

DATA COLLECTION SHEET

Patients diagnosed with CIM and presenting an atypical headache will be requested to participate in their presurgical consultation in HUJT, HUGTiP and HUAdV.

Once they have read and been correctly informed about the study and accepted to participate (with a signed consent form), they will be asked to complete the Data Collection Sheet (see in **Annex 6**).

PRE-SURGICAL VAS SCORE

When having the first visit with the neurosurgeon, the level of patients' headache pain will be evaluated with preoperative VAS score (**Annex 3**).

PRE-SURGICAL DTI APPLICATION

DTI will be performed pre-surgically in or der to evaluate brainstem FA values of patients after they have read and signed DTI consent form (see in **Annex 7**). These values and the size adaptations and placement of all ROI will be performed by 2 radiologist experts from HUJT. All DTI metrics will be analysed and measured in the same way (see in ***5.5.1***).

SURGICAL TECHNIQUE

After patients have been correctly informed by the neurosurgeon about the risks and benefits of PFD and they accept them, surgery will be performed with the same technique (see **Annex 8**).

Neurosurgeons will have to fill out a post-surgical report indicating the surgical procedure that had been carried out. If unexpected complications have arisen this will indicate the direct withdrawal of patients from the study.

FOLLOW-UP

Headache improvement assessments will be conducted approximately 3 months after surgery to avoid post-surgery complications and surgery-related pain.

Patients will be again asked for their post-surgical VAS score and registered in the REDCap database along with all the data collected during the study. The post-surgical VAS scores will be then compared with the pre-surgical scores. The statistical analysis of these results will be useful to evaluate the sensitivity of having higher brainstem FA values to predict good surgical outcome.

Once patients had been evaluated using the VAS score in the follow-up phase, DTI will be again performed in these patients in order to determine if there is an association between changes in FA values with a good surgical outcome.

5.7. FLOW CHART

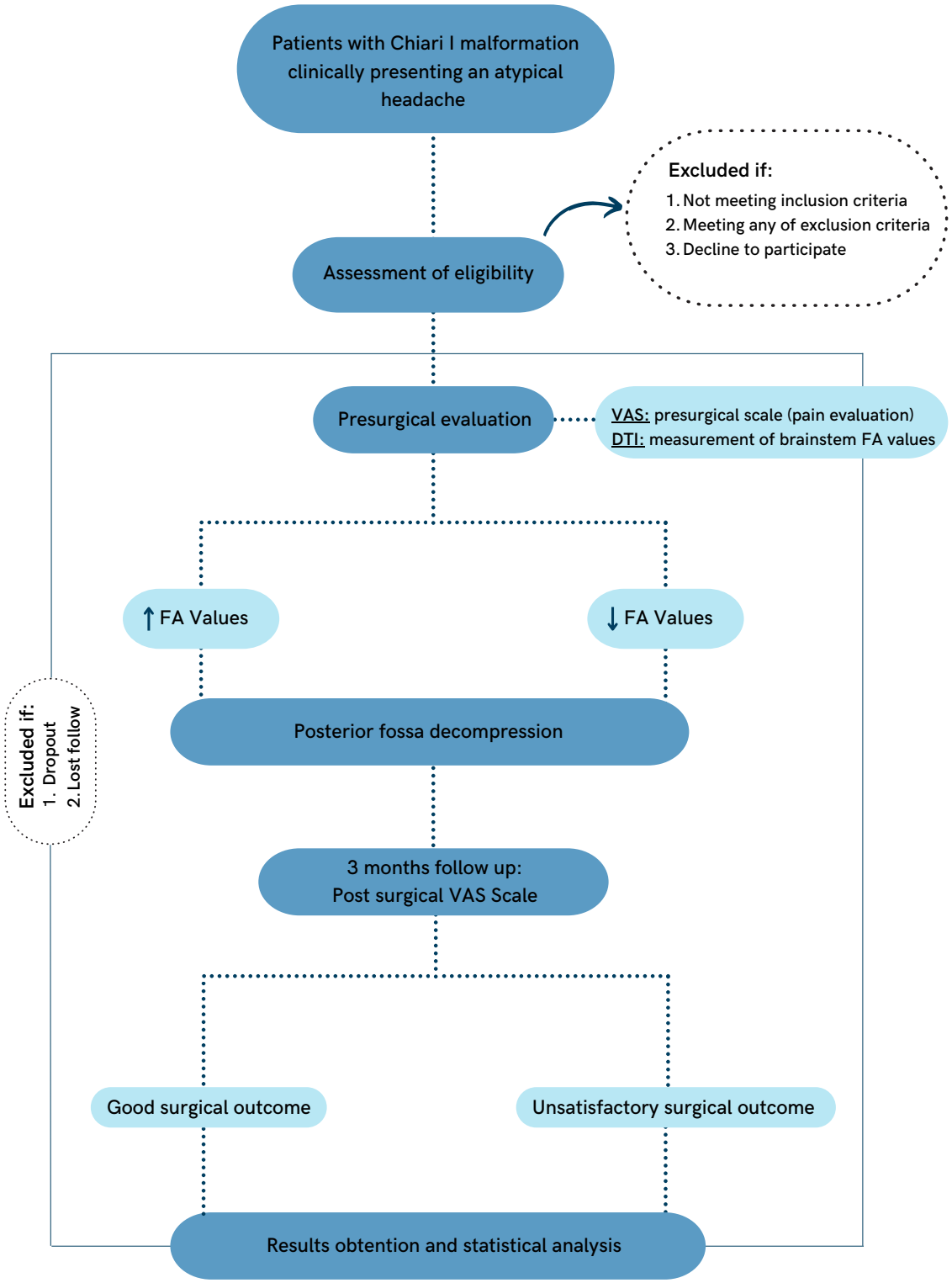


Figure 20: Study flow chart.

6. STATISTICAL ANALYSIS

The statistical analysis will be performed by an expert statistician who will use the Statistical Package for Social Sciences (SPSS) software. We will consider results to be statistically significant if p-values ≤ 0.05 and with confidence intervals of 95%.

6.1. UNIVARIATE/DESCRIPTIVE ANALYSIS

Firstly, a descriptive analysis of the variables will be performed and included in a table. It will vary depending on whether they are qualitative or quantitative (see **table 5**).

The qualitative variables of our study will be summarized using percentages or proportions. For the quantitative variables, being either continuous or discrete, we will use mean and standard deviation (when they follow a Gaussian distribution) or median and interquartile range (when they follow a non-Gaussian distribution).

6.2. BIVARIATE INFERENCE

To ascertain the cut-off point of brainstem FA values which has higher specificity and sensitivity in predicting good surgical outcome, a ROC curve analysis will be made. From this analysis, we will define the brainstem FA value that will be used to consider what are the lower and higher values in this region. Moreover, a cross tabulation (see **table 6**) will be made and sensitivity of having higher values of brainstem FA in predicting good surgical outcome will be calculated, along with the PPV, NPV, LR and DE (or accuracy).

Firstly, it is important to introduce the following concepts in our study (45):

- **True positive (TP):** subjects with higher FA values who will benefit from surgery.
- **False positive (FP):** subjects with higher FA values who will not benefit from surgery.
- **True negative (TN):** subjects with lower FA values who will not benefit from surgery.
- **False negative (FN):** subjects with lower FA values who will benefit from surgery.

Table 6: Cross tabulation of main variables. 2x2 showing results of surgical outcome in columns measured with VAS score (good/unsatisfactory surgical outcome) ; and brainstem FA value in rows (higher/lower brainstem FA values).

	SURGICAL OUTCOME (VAS scale)	
BRAINSTEM FA VALUE in DTI	Good surgical outcome	Unsatisfactory surgical outcome
Higher brainstem FA values	TP	FP
Lower brainstem FA values	FN	TN

The following measurements are obtained from the results of the previous 2x2 table and enables to study the validity of using FA values as a predictive tool for surgical outcome. The internal validity of the study is measured with the sensitivity and specificity; and on the contrary, external validity will be analysed with predictive values.

Table 7: Study measurements. Definition and formula of the measurements that will be used in the study to evaluate the predictive value of DTI.

MEASURES	DEFINITION	FORMULA
SENSITIVITY	Ability to detect patients who will benefit from PFD.	Sensitivity = TP / TP + FN
SPECIFICITY	Ability to detect people who will not benefit from PFD.	Specificity = TN / TN + FP
AREA UNDER THE ROC CURVE (AUC)	Helps to estimate how high is the discriminative power of brainstem FA values in DTI. ○ A perfect diagnostic test has an AUC of 1.0. ○ A non-discriminating test has an AUC of 0.5.	Graph: X-axis = 1-specificity Y-axis = sensitivity
POSITIVE PREDICTIVE VALUE (PPV)	Probability of having a good surgical outcome in a subject with higher brainstem FA value.	PPV = TP / TP + FP

NEGATIVE PREDICTIVE VALUE (NPV)	Probability of not having a good surgical outcome in a subject with a lower brainstem FA value.	NPV = TN / TN + FN
LIKELIHOOD RATIO (LR)	**For a positive test (LR+):** the likelihood of having higher brainstem FA value in patients who will benefit from surgery. Good diagnostic tests have a LR+ > 10	LR + = sensitivity / (1-specificity)
	For a negative test (LR-): the likelihood of having lower brainstem FA in patients who will not benefit from surgery. Good diagnostic tests have a LR- <0,1	LR – = (1-sensitivity) / specificity
DIAGNOSTIC ODDS RATIO (DOR)	It is the ratio of the odds of patients who will benefit from surgery (higher brainstem FA values) relative to the odds in subjects who will not (lower brainstem FA values).	DOR = (TP/FN) / (FP/TN)
DIAGNOSTIC EFFICIENCY (accuracy)	Proportion of correctly classified patients (TP+TN) among all subjects (TP+TN+FP+FN). This parameter is affected by the disease prevalence.	

Moreover, in order to analyse the correlation between our two main variables: FA values (quantitative variable) and surgical outcome (qualitative variable), we will represent the study results in a bar chart.

Additionally, preoperative and postoperative DTI will be compared in a scatter plot to visualise if there is a positive and strong linear relationship between these two quantitative variables. The same analysis will be made to compare preoperative and postoperative VAS score of patients.

Furthermore, the study will contemplate different groups among the participants, that could be reliable to study if there is a significant distinction between them:

- According to age: younger (18-35 years) / older (>35 years)
- According to sex: male / female
- According to pre-surgical VAS score: higher score / lower score

The bivariate comparison of these different groups will be carried out by means of the T-student test for continuous variables (if they follow a parametric distribution) or Mann-Whitney's U (if they follow a non-parametric distribution). For the analysis of categorical variables, chi-squared (χ^2) test will be used or Fisher's exact test when the expected number of counts in one cell will be less than 5.

6.3. MULTIVARIATE ANALYSIS

A trivariate generalized linear mixed models will be performed for jointly modelling prevalence, sensitivities and specificities, which allows us to assess the correlations among these three parameters in our study.

7. ETHICAL ASPECTS

This preliminary study will be submitted to the Clinical Research Ethics Committee of the HUJT, HUGTiP and HUAdV named *Comitè Ètic d'Investigació Clínica,* to be evaluated and approved before the start of the study. Furthermore, it will be conducted in compliance with the latest revision of the Declaration of Helsinki-Medical Research Involving Human Subjects (October 2013) and the Spanish law concerning medical investigation on observational studies *"Ley 14/2007, de 3 de julio, de Investigación Biomédica".*

The ethical principles of Beauchamp and Childress will be respected as follows:

- **Autonomy:** patients' autonomy will be ensured by providing an information sheet and informed consent form (**Annex 4 and 5**). Only those who sign it will be included in the study. These documents will be submitted in advance to the ethics committee for formal approval.
- **Non-maleficence and beneficience:** patients who meet the exclusion criteria will be excluded from the project as they will not benefit from the study procedure; whereas, patients who meet the inclusion criteria will be the ones selected to participate in this study so they will benefit from it.
- **Justice:** all patients who meet both inclusion and exclusion criteria and who have signed the consent form will be considered equally for participation in the study, ensuring a homogeneous and non-discriminatory manner and equality among the individuals.

The confidentiality of all patients in the study will be preserved by anonymizing the data collected. Moreover, data security will be ensured on a locked network which only principal investigators will be able to access. This study will also obey the following laws:

- *"Ley 41/2002 de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica."*
- *"Ley Orgánica 3/2018 de 5 de diciembre, de Protección de Datos personales y garantía de los derechos digitales."*

8. STRENGTHS AND LIMITATIONS

Previous to our study, there are no investigations which specifically study brainstem FA parameters in patients with CIM presenting an atypical headache. Therefore, this is a preliminary study which will enable future large-scale research to achieve further investigation on this topic. Moreover, only studying brainstem FA parameter (specifically, in the medulla oblongata), will provide a more specific and deep investigation in this region, as it is the main area affected by the space conflict due to tonsillar ectopia.

We can expect no DTI measurement bias as images will be acquired at the start of the study and will be interpreted by 2 expert radiologists simultaneously.

Our study presents several limitations that also need to be acknowledged:

- DTI requires an extensive computing power and expertise in the topic. However, the 2 radiologists in the study will be specialized in DTI interpretation.
- Existence of selection bias due to the small and non-probabilistic recruitment of sample chosen in this research. However, the present study might serve for a future multicentric study that would allow performing more precise estimations and therefore, be more representative of the study population.
- As it is a multicentric study, there could be differences between surgical skills as 6 different neurosurgeons will perform PFD, and also errors in data collection and form filling. To avoid this possible variability, all surgeons will have to be correctly informed about the chosen surgical technique. Furthermore, the 3 hospitals have similar capacities and resources to be able to obtain common results.
- The research can be affected by a host of variables, including the different types of atypical headache. Therefore, future research on this topic will be needed, as well as studying other alterations in DTI metrics and in different brain regions. However, some of these variables will be analysed in our study by dividing participants in different groups (see in ***6.2***.).

9. HEALTH IMPACT

Arnold Chiari malformation is a condition that usually occurs in children and young adults. These usually remain asymptomatic, but there are also others with non-specific symptoms, such as headache, which could be not attributed to the malformation itself. Due to this unspecificity of symptoms in some cases the surgical decision becomes a debate among professionals.

Additionally, there is no specific guide for surgical indications when operating this malformation, and the results are sometimes positive but in other cases, patient do not exhibit any improvement. These diverse results have led to the lack of knowledge of what patients can benefit of this intervention and which not.

To date, there is no gold standard test or tool which can predict a good surgical response in patients with CIM. Hence, we believe that this study could provide an answer to whether if diffusion tensor imaging is a useful and novel tool to predict the good surgical outcome of a patient with CIM presenting an atypical headache.

If the hypothesis of our study is confirmed - that is, that brainstem higher values in these patients has a high sensitivity in selecting patients who will have a good surgical evolution - it will foster some changes in the management of these patients that will be favourable for them. Moreover, it will imply a better post-surgical assessment by the neurosurgery team and therefore to reach a common surgical decision and also there will be more surgical beds available for other patients who will really benefit.

On the contrary - if our hypothesis is not confirmed - we consider that DTI could still be useful test in combination with others (such as cine-flow MRI and evoked potentials) to predict surgical outcomes in patients with CIM with a higher sensitivity and specificity. There is a need for future research on the topic.

To sum up, this project opens up the possibility for further studies to consider a change in the surgical selection of patients with CIM and presenting an atypical headache, which represents the main reason for surgical consultation in these patients (70% of the cases). Measuring brainstem FA parameters in DTI may prove to be a useful technique to predict if they would benefit from it and therefore, improve their quality of life.

10. WORK PLAN AND CHRONOGRAM

The study will be conducted in three hospitals: Hospital Universitari Doctor Josep Trueta (Girona), Hospital Universitari Germans Trias i Pujol (Badalona) and Hospital Universitari Arnau de Vilanova (Lleida) and will be composed by the following group of professionals:

- **1 principal investigator** who will take care of the elaboration of the protocol and in charge of the study; the typewriting of preoperative and postoperative VAS score, as well as scanning the information sheet and consent form to bring up to date or databases. Therefore, she/he will be responsible of the data collection of the study and to present it to the statistician.
- **2 radiologists** from Hospital Josep Trueta who will analyse all DTI at the start and in the end of the study.
- **6 neurosurgeons,** 2 from each hospital (HUJT, HUGTiP and HUAdV) who will perform the surgical technique of PFD previously stipulated.
- **1 statistician** from the Institut d'Investigació Biomèdica de Girona (IdibGi) who will perform the statistical analysis.

10.1. WORK PLAN

The study will last approximately 27 months, from November 2022 to February 2025, and will be divided into 8 stages (see **table 8**):

STAGE 0: **Elaboration of the protocol design** (November 2022-January 2023)

Protocol elaboration will be the first item presented. Once it has been done an extensive bibliographic research on the topic, hypothesis and objectives of the study will be designed in order to create an adequate protocol design. It will be the responsibility of the principal investigator of the study. This phase will last approximately 2 months.

STAGE 1: **Ethical evaluation** (February 2023)

Once the protocol has been done, it will have to be evaluated and accepted by the Comitè d'Ètica d'Investigació Clínica (CEIC) of HUJT, HUGTiP and HUAdV.

STAGE 2: **Coordination and training** (March 2023)

Once the protocol is approved, training workshops will be done for all professionals that will participate in our study (statisticians, radiologists and neurosurgeons) in order to unify and standardize intervention and avoid bias.

STAGE 3: **Information to patients and informed consent** (March 2023)

Patients in the pre-surgical neurosurgery consultation who meet the inclusion criteria will be contacted and invited to participate in the study. If they are interested, an information sheet and consent form will be provided to them so that they are correctly informed and able to decide if they want to take part of it or not. Only those who signed it will be part of the study.

STAGE 4: **Data collection** (March 2023-March 2024)

The approximate duration of participants recruitment is about 1 year.

After having recruited the study participants with their consent form signed and making sure they understood the purpose of their participation in the study, patients will have to fulfill the Data Collection Sheet (**Annex 6**). All at once they will have their first visit with the neurosurgeon in HUJT, HUGTiP or HUAdV, in which their headache pain intensity will be evaluated and scored from 0 to 100mm with the VAS scale. Moreover, they will be given an appointment with the radiologist to undergo DTI at the same hospital.

Brainstem FA parameters in DTI will be analysed and interpreted by two radiologists in HUJT at the same way (see in ***5.5.1***).

Once they had undergone DTI test, they will have a second visit with the neurosurgeon, who will inform about the risks and benefits of PFD and will provide a consent form (see **Annex 2**). When this document is signed, PFD will be performed.

STAGE 5: **Surgical intervention** (April 2024-July 2024)

The surgical intervention will be carried out by 6 neurosurgeons of HUJT, HUGTiP and HUAdV. These professionals will be informed about the way patients will have to be operated, since they will all require the same technique (see **Annex 8**).

STAGE 6: **Follow-up** (July-October 2024)

The follow-up will be made 3 months post-surgery to avoid post-surgery complications and surgery-related pain. In this phase, headache pain intensity will be reevaluated with the VAS scale. The score of every patient will be compared with the pre-surgical VAS score. Thus, we will then group patients in two depending on their pain improvement: "good surgical outcome" and "unsatisfactory surgical outcome".

At the follow-up visit, a DTI will be again performed to evaluate whether if changes in postoperative FA values is correlated with having a good surgical outcome.

STAGE 7: **Data analysis** (October-December 2024)

With the results of their post-surgical VAS scale and the pre-surgical DTI results, the sensitivity of brainstem FA parameters will be assessed along with other measurements to ensure its validity (see **table 5**).

Statistical analysis will be performed by a specialized statistician. After that, the results will be given to the principal investigator.

STAGE 8: **Publication of results** (December 2024-February 2025)

Results will be written in an article by the principal investigator and will be further edited and published. This phase will last about 2 months.

10.2. CHRONOGRAM

Table 8: Chronogram.

STUDY PHASES	2022		2023												2024												2025		
	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
PROTOCOL DESIGN																													
ETHICAL EVALUATION																													
COORDINATION AND TRAINING																													
INFORMATION TO PATIENTS AND INFORMED CONSENT																													
DATA COLLECTION																													
SURGICAL INTERVENTION																													
FOLLOW-UP																													
DATA ANALYSIS																													
PUBLICATION OF RESULTS																													

Stage 0
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
Stage 8

11. BUDGET

PERSONNEL EXPENSES

- The **main research team** is composed by 6 neurosurgeons and 2 radiologists who work in the hospitals participating in the study. For this reason, it will not imply an additional cost, as they will perform their duties as part of their work activity. However, the radiologists will have to interpret DTI sequence of patients and give detailed information about FA parameters in a specific ROI. This will imply extra-time in their routine daily work but still as they are part of the main research team they would not be extra payed.
- **A qualified statistician** from IdibGi who will carry out the statistical analysis will receive 30€/h and working 65h in a month for three months, it will cost 5.850€.

MATERIAL COSTS

- **Printing costs** (includes information sheet and consent form of the study): for a sample of 39 patients, we will print 39 information sheets and informed consent double-sided sheets at 0,10€ per copy with a total of 7,8€.
- **DTI sequence:** the total cost of DTI for a 1.5-T system is 329,00€. DTI will be performed at the start and at the end of the study in each patient. However, it will not suppose an additional cost as pre-operative and post-operative MRI are usually done in these patients. Even though, radiologists who will interpret DTI images will be extra paid as it is not part of their normal work activity when assessing a MRI of CIM patient.

RESULTS DISSEMINATION COSTS

- **Publication fees:** 1.000€ to publish in a journal article.
- **Congresses registration:** 800€ for national congresses attendance and 1.600€ for international congresses attendance.

Table 9: Study's budget.

ITEM		AMOUNT	COST	SUBTOTAL	TOTAL
PERSONNEL EXPENSES					
Main investigators (neurosurgeons and radiologists)		-	0€	0€	**5.850€**
Statistician		65h/month during 3 months	30€/h	5.850€	
MATERIAL COSTS					
Printing materials (information sheet and consent form)		78 copies	0,10€/copy	7,8€	**7,8€**
DTI sequence		78 DTI's	0€	0€	
RESULTS DISSEMINATION COSTS					
Publication fees		-	1.000€	1.000€	**3.400€**
Congresses registration	**National Congresses**	-	800€	800€	
	International Congresses	-	1.600€	1.600€	
				TOTAL	**9.257,8€**

12. FEASIBILITY

We consider that our study is feasible to carry out as there are no major obstacles to its implementation:

- 1 year is sufficient to recruit patients needed for our study in the 3 hospitals participating in the study.
- The three hospitals participating in the study provide the tools and experience needed to carry out the study.
- SAP and REDCap systems are a structured database where all clinical information and imaging studies of patients can be uploaded and shared with all the data required for the study.
- The study will be performed by 2 radiologists simultaneously, who will interpret all DTI images will be made with the same commercial image viewing software.
- PFD will be accomplished by 6 neurosurgeons in HUJT, HUGTiP and HUAdV specialized in CIM. They will all receive the same information about the surgical procedure which should be done in a homogeneously way to all patients.
- Statistical analysis will be carried out by professional statistician from IdibGi who will have more than 15 years of experience. Statistical analysis will be made with SPSS program, which is a comprehensive statistical software.
- The study will be made within approximately 2 years to avoid the emergence of new studies evaluating similar or same objectives in our study, which will suppose the end of the study or to assume its futility.

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14. ANNEXES

ANNEX 1. Diagnosis criteria of Arnold's Chiari headache. Adapted from (6).

International classification of headache disorders criteria for the diagnosis of headache attributed to Chiari I Malformation.

A. Headache fulfilling criterion C

B. CIM has been demonstrated

1. 5mm or greater cerebellar tonsillar herniation below the foramen magnum.
2. 3mm cerebellar tonsillar herniation + crowding of subarachnoid space at the craniocervical junction as evidenced by compression of the CSF spaces posterior and lateral to the cerebellum.
3. Reduced height of the superior part of the occipital lobe, or increased slope of the tentorium or kinking of the medulla.

C. Evidence of causation demonstrated by at least 2 of the following

1. Either or both of the following
   a. Headache has developed in temporal relation to CIM.
   b. Headache has resolved within 3 months after successful treatment of the CIM.
2. Headache has at least one of the following 3 characteristics
   a. Precipitated by cough or other Valsalva-like manoeuvre
   b. Occipital or suboccipital location
   c. Lasting less than 5 minutes.
3. Headache is associated with other symptoms and/or clinical signs of brainstem, cerebellar, lower cranial nerve, and/or cervical spinal cord dysfunction.

D. Not better accounted for by another headache disorder diagnosis.

CSF: cerebrospinal fluid; CIM: Chiari I Malformation.

ANNEX 2. Posterior fossa decompression consent form extracted from (46).

Queensland Government

Posterior Fossa Decompression

Facility:

(Affix identification label here)

URN:

Family name:

Given name(s):

Address:

Date of birth: Sex: ☐ M ☐ F ☐ I

A. Interpreter / cultural needs

An Interpreter Service is required?	☐ Yes	☐ No
If *Yes*, is a qualified Interpreter present?	☐ Yes	☐ No
A Cultural Support Person is required?	☐ Yes	☐ No
If *Yes*, is a Cultural Support Person present?	☐ Yes	☐ No

B. Condition and treatment

The doctor has explained that you have the following condition: *(Doctor to document in patient's own words)*

.....

.....

This condition requires the following procedure. *(Doctor to document - include site and/or side where relevant to the procedure)*

.....

.....

A posterior fossa decompression procedure is performed to relieve pressure at the base of the brain. It is used for the treatment and management of cerebellar strokes, bleeds, tumours and Chiari malformation.

C. Risks of posterior fossa decompression

There are risks and complications with this procedure. They include but are not limited to the following.

Common risks and complications (more than 5%) include:

- Infection, requiring antibiotics and further treatment.
- Minor pain, bruising and/or infection from IV cannula site. This may require antibiotics.
- Bleeding is more common if you have been taking blood thinning drugs such as anticoagulants (eg warfarin, dabigatran, rivaroxaban), antiplatelets (eg aspirin, clopidogrel, dipyridamole) or supplements like fish oil.
- Post-operative vomiting is likely to occur requiring treatment with medication.
- Fluid leakage from around the brain may occur through the wound after the operation. This may require further surgery.

Uncommon risks and complications (1-5%) include:

- Heart attack due to the strain on the heart.
- Stroke or stroke like complications may occur causing neurological deficits such as weakness in the face, arms and legs. This could be temporary or permanent.
- Build up of fluid within the brain (Hydrocephalus) requiring a temporary drain or permanent shunt. This may be temporary or permanent.
- The problem may not be cured by surgery. This may require further treatment.
- Ongoing deterioration in symptoms including neck pain, despite decompression. This may be temporary or permanent.
- Visual disturbance. This may be temporary or permanent.
- Decrease in the normal body salt concentration. This may require admission to intensive care and further treatment.
- Skull deformity and/or poor cosmetic result may occur requiring further surgery at a later stage.
- Small areas of the lung may collapse, increasing the risk of chest infection. This may need antibiotics and physiotherapy.
- Increase risk in obese people of wound infection, chest infection, heart and lung complications, and thrombosis.
- Blood clot in the leg (DVT) causing pain and swelling. In rare cases part of the clot may break off and go to the lungs.

Rare risks and complications (less than 1%) include:

- Instability of the spine or abnormal alignment may occur requiring further surgery.
- Inability to talk due to cerebellar mutism. This is usually temporary.
- Inability to breathe when asleep. This may require long term ventilation.
- Death as a result of this procedure is very rare.

D. Significant risks and procedure options

(Doctor to document in space provided. Continue in Medical Record if necessary.)

.....

.....

E. Risks of not having this procedure

(Doctor to document in space provided. Continue in Medical Record if necessary.)

.....

.....

F. Anaesthetic

This procedure may require an anaesthetic. *(Doctor to document type of anaesthetic discussed)*

.....

.....

DO NOT WRITE IN THIS BINDING MARGIN

PROCEDURAL CONSENT FORM

v2.00 – 10/2013
SW9072

Queensland Government

Posterior Fossa Decompression

Facility:

(Affix identification label here)

URN:

Family name:

Given name(s):

Address:

Date of birth: Sex: ☐ M ☐ F ☐ I

G. Patient consent

I acknowledge that the doctor has explained;

- my medical condition and the proposed procedure, including additional treatment if the doctor finds something unexpected. I understand the risks, including the risks that are specific to me.
- the anaesthetic required for this procedure. I understand the risks, including the risks that are specific to me.
- other relevant procedure/treatment options and their associated risks.
- my prognosis and the risks of not having the procedure.
- that no guarantee has been made that the procedure will improve my condition even though it has been carried out with due professional care.
- the procedure may include a blood transfusion.
- tissues and blood may be removed and could be used for diagnosis or management of my condition, stored and disposed of sensitively by the hospital.
- if immediate life-threatening events happen during the procedure, they will be treated based on my discussions with the doctor or my Acute Resuscitation Plan.
- a doctor other than the consultant may conduct the procedure. I understand this could be a doctor undergoing further training.

I have been given the following Patient Information Sheet/s:

- ☐ **About Your Anaesthetic**
- ☐ **Posterior Fossa Decompression**
- ☐ **Blood & Blood Products Transfusion**

- I was able to ask questions and raise concerns with the doctor about my condition, the proposed procedure and its risks, and my treatment options. My questions and concerns have been discussed and answered to my satisfaction.
- I understand I have the right to change my mind at any time, including after I have signed this form but, preferably following a discussion with my doctor.
- I understand that image/s or video footage may be recorded as part of and during my procedure and that these image/s or video/s will assist the doctor to provide appropriate treatment.

On the basis of the above statements,

I request to have the procedure

Name of Patient:

Signature:

Date:

Patients who lack capacity to provide consent

Consent must be obtained from a substitute decision maker/s in the order below.

Does the patient have an Advance Health Directive (AHD)?

☐ Yes ▶ Location of the original or certified copy of the AHD:

☐ No ▶ Name of Substitute Decision Maker/s:

Signature:

Relationship to patient:

Date: PH No:

Source of decision making authority (tick one):

- ☐ Tribunal-appointed Guardian
- ☐ Attorney/s for health matters under Enduring Power of Attorney or AHD
- ☐ Statutory Health Attorney
- ☐ If none of these, the Adult Guardian has provided consent. Ph 1300 QLD OAG (753 624)

H. Doctor/delegate statement

I have explained to the patient all the above points under the Patient Consent section (G) and I am of the opinion that the patient/substitute decision-maker has understood the information.

Name of Doctor/delegate:

Designation:

Signature:

Date:

I. Interpreter's statement

I have given a sight translation in

(state the patient's language here) of the consent form and assisted in the provision of any verbal and written information given to the patient/parent or guardian/substitute decision-maker by the doctor.

Name of Interpreter:

Signature:

Date:

DO NOT WRITE IN THIS BINDING MARGIN

02/2011 – v2.00

Queensland Government

Consent Information - Patient Copy
Posterior Fossa Decompression

1. What is a posterior fossa decompression?

A posterior fossa decompression procedure is performed to relieve pressure at the base of the brain. It is used for the treatment and management of cerebellar strokes, bleeds, tumours and Chiari malformation.

The procedure involves a cut being made into the tissues at the back of the head and the neck bones covering the base of the brain.

A small section of bone is removed from the base of the skull and at times from the upper spine. In many conditions this is all that is required.

However, for conditions such as bleeding and tumour, the lining of the cerebellum will be opened. The clot or tumour will be removed.

The opening will be closed either using a tissue graft taken from a separate cut in your thigh or with a synthetic material.

The removed skull bone is not usually put back in place. The cut is closed with sutures or clips.

2. My anaesthetic

This procedure will require a general anaesthetic.

See **About Your Anaesthetic information sheet** for information about the anaesthetic and the risks involved. If you have any concerns, discuss these with your doctor.

If you have not been given an information sheet, please ask for one.

3. What are the risks of this specific procedure?

There are risks and complications with this procedure. They include but are not limited to the following.

Common risks and complications (more than 5%) include:

- Infection, requiring antibiotics and further treatment.
- Minor pain, bruising and/or infection from IV cannula site. This may require antibiotics.
- Bleeding is more common if you have been taking blood thinning drugs such as anticoagulants (eg warfarin, dabigatran, rivaroxaban), antiplatelets (eg aspirin, clopidogrel, dipyridamole) or supplements like fish oil. Check with the treating doctor or relevant clinical staff if any medication you are taking, that is not list here, acts like a blood thinner.
- Post-operative vomiting is likely to occur requiring treatment with medication.
- Fluid leakage from around the brain may occur through the wound after the operation. This may require further surgery.

Uncommon risks and complications (1-5%) include:

- Heart attack due to the strain on the heart.
- Stroke or stroke like complications may occur causing neurological deficits such as weakness in the face, arms and legs. This could be temporary or permanent.
- Build up of fluid within the brain (Hydrocephalus) requiring a temporary drain or permanent shunt. This may be temporary or permanent.
- The problem may not be cured by surgery. This may require further treatment.
- Ongoing deterioration in symptoms including neck pain, despite decompression. This may be temporary or permanent.
- Visual disturbance. This may be temporary or permanent.
- Decrease in the normal body salt concentration. This may require admission to intensive care and further treatment.
- Skull deformity and/or poor cosmetic result may occur requiring further surgery at a later stage.
- Small areas of the lung may collapse, increasing the risk of chest infection. This may need antibiotics and physiotherapy.
- Increase risk in obese people of wound infection, chest infection, heart and lung complications, and thrombosis.
- Blood clot in the leg (DVT) causing pain and swelling. In rare cases part of the clot may break off and go to the lungs.

Rare risks and complications (less than 1%) include:

- Instability of the spine or abnormal alignment may occur requiring further surgery.
- Inability to talk due to cerebellar mutism. This is usually temporary.
- Inability to breathe when asleep. This may require long term ventilation.
- Death as a result of this procedure is very rare.

Notes to talk to my doctor about:

.....

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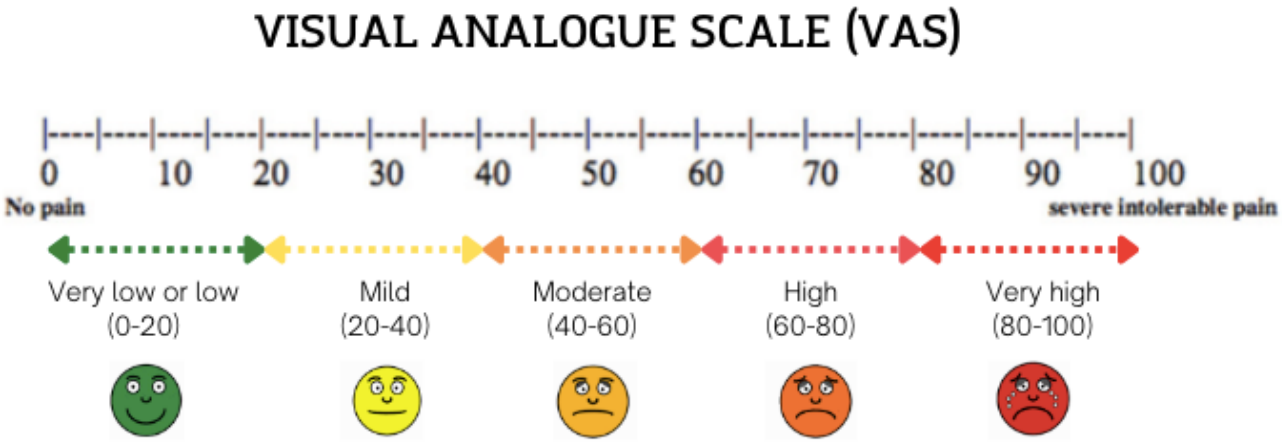
ANNEX 3. The Visual Analogue Scale evaluating pain from 0-100mm. Adapted from (47).



ANNEX 4. Information sheet.

FULL D'INFORMACIÓ PER A LA PACIENT

TÍTOL DE L'ESTUDI	Predicció dels resultats postoperatoris en la malformació de Chiari tipus I presentada clínicament amb una cefalea atípica amb valors d'anisotropia fraccionada del tronc cerebral.
INVESTIGADOR PRINCIPAL	Gemma-Júlia De Manuel-Rimbau Milla
CENTRE	☐ Hospital Universitari Dr. Josep Trueta (Girona) ☐ Hospital Universitari Germans Trias i Pujol (Badalona) ☐ Hospital Universitari Arnau de Vilanova (Lleida)

INTRODUCCIÓ

Ens dirigim a vostè per a informar-li sobre un estudi d'investigació en el qual se'l convida a participar, el qual ha estat aprovat pel Comitè d'Ètica i Investigació Clínica.

La intenció d'aquest document és donar-li tota la informació de manera correcta, clara i precisa per a què pugui decidir si accepta o no participar en l'estudi. Així doncs, li demanem que llegeixi aquest document atentament i que ens consulti qualsevol dubte que li sorgeixi.

PARTICIPACIÓ VOLUNTÀRIA

El convidem a participar en aquest estudi ja que ha estat recentment diagnosticat de la malformació de Chiari tipus I.

La seva participació en aquest estudi és totalment voluntària i en tot moment pot decidir o no participar o retirar-se d'aquest un cop estigui dins, sense que això suposi un canvi en la seva atenció sanitària.

OBJECTIUS DE L'ESTUDI

Aquest estudi pretén resoldre principalment un objectiu: avaluar el valor predictiu positiu de tenir valors alts d'anisotropia fraccionada en la prova d'imatge Diffusion Tensor Imaging (DTI) en predir un bon resultat quirúrgic en pacients amb la malformació de Chiari tipus I que presentin una cefalea com la de vostè.

DESCRIPCIÓ DE L'ESTUDI

L'estudi inclourà un total de 39 participants que seran els suficients per a poder resoldre el nostre objectiu principal. Aquests hauran estat diagnosticats prèviament de la malformació de Chiari tipus I per un neurocirurgià o neuròleg.

Aquests pacients s'informen en la consulta pre-quirúrgica i són convidats a participar en l'estudi. Previ a la cirurgia, seran avaluats de la seva cefalea i aquesta serà puntuada subjectivament del 0-100mm amb l'escala analgèsica del dolor.

Per a l'avaluació de l'objectiu principal descrit anteriorment, els pacients seran dividits en dos grups després de l'obtenció dels resultats de la prova DTI:

- Pacients amb valors alts d'anisotropia fraccionada
- Pacients amb valors baixos d'anisotropia fraccionada

3 mesos després de la cirurgia es valorarà la milloria o la no milloria de la cefalea amb la mateixa escala utilitzada anteriorment.

ACTIVITATS DE L'ESTUDI

La seva participació en aquest projecte tindrà una durada de 19 mesos, en el qual tindrà:

- Llegir atentament i signar el consentiment informat en el cas que vulgui participar.
- 1 visita amb el neurocirurgià per valorar la intensitat de la cefalea que presenta amb una escala analgèsica del dolor.
- 1 visita amb el radiòleg/radiòloga per a fer la prova DTI un cop s'ha diagnosticat de Chiari tipus I.
- 1 visita prèvia a l'operació amb el neurocirurgià per a què li expliqui el procediment i els seus riscos i beneficis.
- Intervenció quirúrgica (descompressió de la fossa posterior).
- Seguiment als 3 mesos post-cirurgia per a reavaluar la intensitat del dolor que presenta amb l'escala analgèsica del dolor.
- Una altra visita amb el radiòleg per repetir la DTI.

RISCS I BENEFICIS

La DTI és una prova que no comporta cap risc directe a nivell de salut i és segura en aquells pacients en els quals no està contraindicada.

La majoria dels pacients després de la cirurgia clínicament milloren. La descompressió de la fossa posterior no és complicada, però que com tota cirurgia comporta certs riscs:

- **Riscs i complicacions freqüents (>5%):** infecció, dolor cervical lleu, hemorràgia, nàusees i vòmits, fuga de líquid cefaloraquidi a través de la ferida.
- **Riscs i complicacions infreqüents (1-5%):** infart a causa de la tensió del cor, complicacions semblant a un ictus o un ictus que provoquin dèficits neurològics com ara debilitat a la cara, braços i cames, hidrocefàlia (acumulació de líquid dins del cervell), deteriorament continu dels símptomes, trastorns visuals, disminució de la deformitat del crani i/o un mal resultat estètic, complicacions cardíaques i pulmonars, trombosi, trombosi venosa profunda que pot arribar a tromboembolisme pulmonar.
- **Riscs i complicacions molt infreqüents (<1%):** inestabilitat de la columna o mal alineament, incapacitat de parlar a causa del mutisme cerebel·lar (sol ser temporal), incapacitat per respirar durant el son. Finalment, la mort com a conseqüència d'aquest procediment és molt rara.

Els pacients hauran d'avisar al seu metge si presenten els següents símptomes després de la cirurgia: cefalea que no cedeix amb medicaments, febre (>38ºC), nàusees i vòmits, signes d'infecció de ferida (envermelliment, dolor,...), rigidesa de coll, debilitat/entumiment, somnolència o problemes d'equilibri.

Gràcies a la seva participació, en un futur es podrà predir si un pacient amb la mateixa malformació que vostè es beneficiarà o no de la cirurgia i per tant, reduirem l'exposició al risc que comporta tota cirurgia i evitarem ser menys agressius en el tractament d'aquests pacients.

CONTACTE EN CAS DE DUBTE

Si durant la seva participació té algun dubte o necessita obtenir més informació, pot posar-se en contacte amb el seu cirurgià i amb la investigadora principal. Se li proporcionarà un paper amb les dades de contacte.

PROTECCIÓ DE DADES PERSONALS

Tant els responsables de l'estudi com el centre s'asseguraran del compliment de tots els principis contemplats en la normativa de protecció de dades nacional i europea. Les seves dades seran accessibles només pels membres de l'equip de recerca i s'afegiran a la base de dades de forma anònima.

ANNEX 5. Consent form.

CONSENTIMENT INFORMAT

TÍTOL DE L'ESTUDI	Predicció dels resultats postoperatoris en la malformació de Chiari tipus I presentada clínicament amb una cefalea atípica amb valors d'anisotropia fraccionada del tronc cerebral.
INVESTIGADOR PRINCIPAL	Gemma-Júlia De Manuel-Rimbau Milla
CENTRE	☐ Hospital Universitari Dr. Josep Trueta (Girona) ☐ Hospital Universitari Germans Trias i Pujol (Badalona) ☐ Hospital Universitari Arnau de Vilanova (Lleida)

Jo, _____ (nom i cognoms participant),

amb DNI/passaport _____:

- ☐ He llegit i entès el full d'informació que se m'ha entregat sobre l'estudi.
- ☐ He pogut fer les preguntes pertinents sobre l'estudi i s'han respost satisfactòriament.
- ☐ He rebut suficient informació sobre l'estudi.
- ☐ Entenc que la meva participació és voluntària i que em puc retirar en qualsevol moment.
- ☐ Signo aquest document de consentiment de manera voluntària per manifestar el meu dret de participar en aquest estudi de recerca.

Presto la meva conformitat per a participar a l'estudi i confirmo que he llegit el full d'informació i estic conforme amb el seu contingut:

Firma de la participant:

Data: ___/___/___

Firma de l'investigador:

Data: ___/___/___

ANNEX 6. Data Collection Sheet.

FULL DE RECOL·LECCIÓ DE DADES

TÍTOL DE L'ESTUDI	Predicció dels resultats postoperatoris en la malformació de Chiari tipus I presentada clínicament amb una cefalea atípica amb valors d'anisotropia fraccionada del tronc cerebral.
INVESTIGADOR PRINCIPAL	Gemma-Júlia De Manuel-Rimbau Milla
CENTRE	☐ Hospital Universitari Dr. Josep Trueta (Girona) ☐ Hospital Universitari Germans Trias i Pujol (Badalona) ☐ Hospital Universitari Arnau de Vilanova (Lleida)

CO-VARIABLES

Sexe	☐ Home ☐ Dona
Edat	_____ anys
Antecedents mèdics potencialment relacionats amb cefalea	☐ Ansietat ☐ Depressió ☐ Migranya ☐ Cefalea tensional ☐ Cefalees trigemino-autonòmiques ☐ Arteritis de la temporal / de Horton ☐ Hipotensió / hipertensió intracranial ☐ Hipertensió arterial ☐ Neuràlgia del trigèmin ☐ Altres: Especifica quina _____

Ètnia	☐ Africana ☐ Asiàtica ☐ Caucàsica ☐ Llatino-Amèrica ☐ Altres: Especifica quina _____
Aparició de la cefalea	☐ Fa menys de 3 mesos ☐ Fa més de 3 mesos

DADES DELS RESULTATS DE L'ESCALA ANALÒGICA VISUAL (escala del dolor 0-100mm)

Valor pre-quirúrgic en l'escala VAS: _____ mm

Valor post-quirúrgic en l'escala VAS: _____ mm

DADES DELS RESULTATS DE LA DTI PRE-QUIRÚRGICA

☐ Pacient amb valors alts d'anisotropia fraccionada en el tronc de l'encèfal.

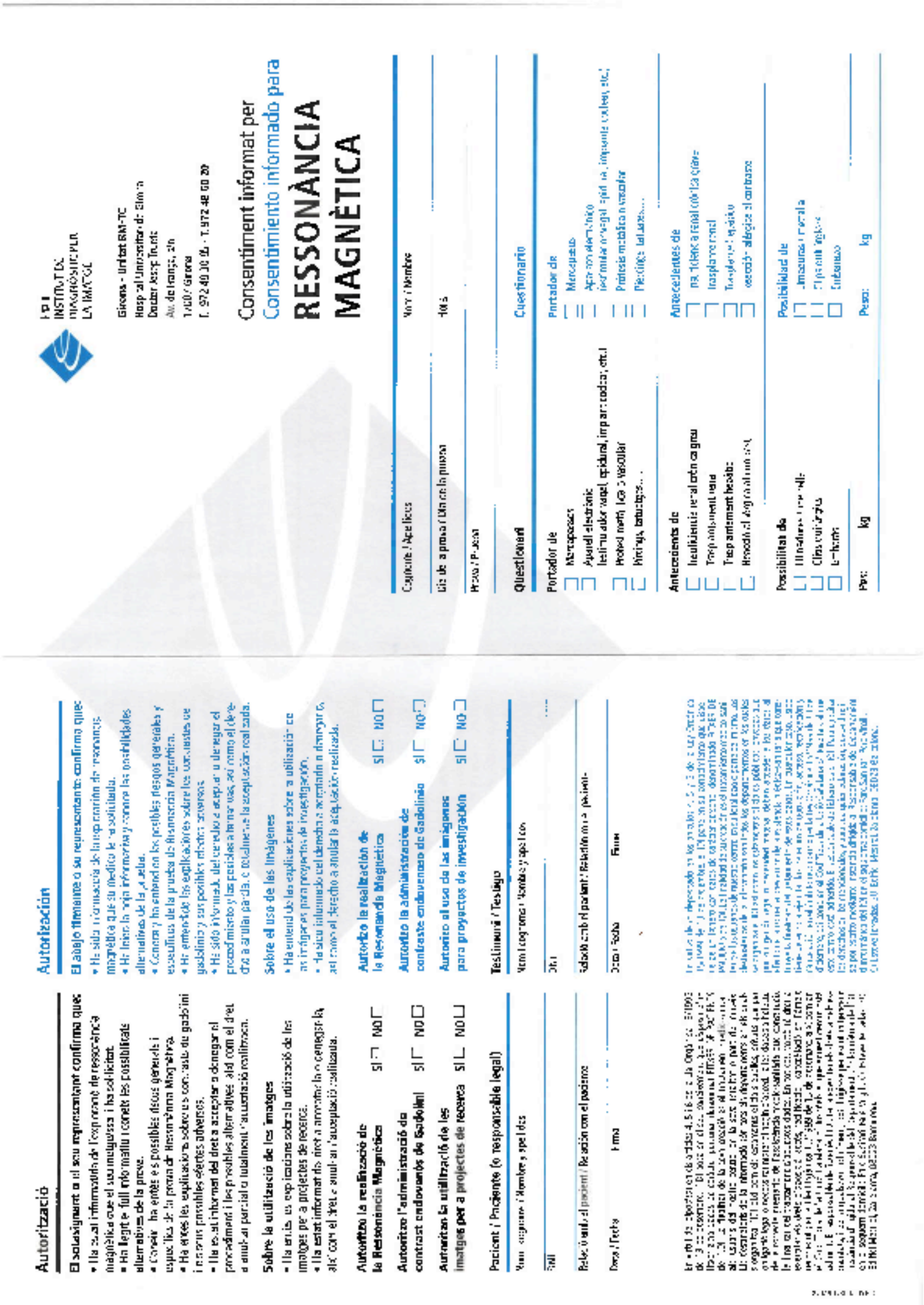
☐ Pacient amb valors baixos d'anisotropia fraccionada en el tronc de l'encèfal.

DADES DELS RESULTATS DE LA DTI POST-QUIRÚRGICA

☐ Pacient amb valors alts d'anisotropia fraccionada en el tronc de l'encèfal.

☐ Pacient amb valors baixos d'anisotropia fraccionada en el tronc de l'encèfal.

ANNEX 7. DTI consent form (same as MRI consent form).



IDI
INSTITUT DE DIAGNÒSTIC PER LA IMATGE

Girona - Unitat RM-TC
Hospital Universitari de Girona Doctor Josep Trueta
Av. de França, s/n
17007 Girona

Consentiment informat per
Consentimiento informado para
RESSONÀNCIA MAGNÈTICA

Cognoms / Apellidos — Nom / Nombre
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Prova / Prueba

Qüestionari / **Cuestionario**

Portador de / Portador de
- Marcapassos / Marcapasos
- Aparell electrònic (estimulador vagal, epidural, implant coclear, etc.) / Aparato electrónico (estimulador vagal, epidural, implante coclear, etc.)
- Pròtesi metàl·lica o vascular / Prótesis metálica o vascular
- Pírcings, tatuatges... / Piercings, tatuajes...

Antecedents de / Antecedentes de
- Insuficiència renal crònica greu / Insuficiencia renal crónica grave
- Trasplantament renal / Trasplante renal
- Trasplantament hepàtic / Trasplante hepático
- Reacció al·lèrgica al contrast / Reacción alérgica al contraste

Possibilitat de / Posibilidad de
- Claustrofòbia / Claustrofobia
- Clips quirúrgics / Clips quirúrgicos
- Embaràs / Embarazo

Pes: kg / Peso: kg

Autorització / **Autorización**

El sotasignant o el seu representant confirma que: / El abajo firmante o su representante confirma que:
- Ha estat informat/da de l'exploració de ressonància magnètica que el seu metge/ssa li ha sol·licitat. / Ha sido informado/a de la exploración de resonancia magnética que su médico le ha solicitado.
- Ha llegit el full informatiu i coneix les possibilitats alternatives de la prova. / Ha leído la hoja informativa y conoce las posibilidades alternativas de la prueba.
- Coneix i ha entès els possibles riscos generals i específics de la prova de Ressonància Magnètica. / Conoce y ha entendido los posibles riesgos generales y específicos de la prueba de Resonancia Magnética.
- Ha entès les explicacions sobre els contrastos de gadolini i els seus possibles efectes adversos. / Ha entendido las explicaciones sobre los contrastes de gadolinio y sus posibles efectos adversos.
- Ha estat informat del dret a acceptar o denegar el procediment i les possibles alternatives, així com el dret a anul·lar parcial o totalment l'acceptació realitzada. / Ha sido informado del derecho a aceptar o denegar el procedimiento y las posibles alternativas, así como el derecho a anular parcial o totalmente la aceptación realizada.

Sobre la utilització de les imatges / Sobre el uso de las imágenes
- Ha entès les explicacions sobre la utilització de les imatges per a projectes de recerca. / Ha entendido las explicaciones sobre la utilización de las imágenes para proyectos de investigación.
- Ha estat informat del dret a acceptar-la o denegar-la, així com el dret a anul·lar l'acceptació realitzada. / Ha sido informado del derecho a aceptarla o denegarla, así como el derecho a anular la aceptación realizada.

Autoritzo la realització de la Ressonància Magnètica SÍ ☐ NO ☐ / Autorizo la realización de la Resonancia Magnética SÍ ☐ NO ☐
Autoritzo l'administració de contrast endovenós de Gadolini SÍ ☐ NO ☐ / Autorizo la administración de contraste endovenoso de Gadolinio SÍ ☐ NO ☐
Autoritzo la utilització de les imatges per a projectes de recerca SÍ ☐ NO ☐ / Autorizo el uso de las imágenes para proyectos de investigación SÍ ☐ NO ☐

Pacient / Paciente (o responsable legal)
Nom i cognoms / Nombre y apellidos
DNI
Relació amb el pacient / Relación con el paciente
Data / Fecha — Firma

Testimoni / Testigo
Nom i cognoms / Nombre y apellidos
DNI
Relació amb el pacient / Relación con el paciente
Data / Fecha — Firma

Què és la Ressonància Magnètica (RM)?

• És una de les tècniques de diagnòstic per la imatge més modernes e innòcues. Mitjançant un potent imant i ones de ràdio s'obtenen imatges del cos humà.
• No utilitza Raigs X ni elements radioactius.
• No té efectes nocius demostrats.
• Durant l'estudi d'RM, el metge i tècnic de la sala de control us parlaran i us controlaran a través d'un monitor. Disposeu d'un avisador dins de l'aparell per si necessiteu avisar al personal. Durant el procediment, el personal vetllarà al màxim pel vostre confort.

Precaucions

• Cal que us informeu sobre la necessitat o no d'estar en dejú. Especialment si és l'RM d'un nadó o nen (per si fos necessari sedar-lo) o en els adults que es facin una RM abdominal.
• Comunigueu al personal sanitari si patiu al·lèrgies conegudes.
• Comunigueu al personal sanitari si sou portadors d'objectes metàl·lics o electrònics.
• Entreu a la sala sense objectes metàl·lics.
• Per concretar el diagnòstic pot ser necessari administrar contrast endovenós. En aquest cas us informaran prèviament.
• Aporteu la màxima informació clínica de que disposeu, així com altres proves que us hagin fet (Rx, TC o RM, sobretot si s'han realitzat a altres centres).

Marcapàs i aparells electrònics

• Donat el risc de lesió i de mal funcionament del propi aparell, no es pot entrar a la sala amb marcapàs cardiac, estimuladors electrònics o determinades pròtesis.
• Abans d'entrar a la sala s'ha de notificar al personal si s'és portador d'aparells electrònics i es valorarà la compatibilitat amb la màquina de ressonància.

Embaràs

• Tot i que no s'han demostrat efectes nocius de l'RM sobre el fetus, és recomanable que es notifiqui si la pacient està embarassada. En certes ocasions es pot valorar clínicament la idoneïtat de l'estudi.

IDI
INSTITUT DE DIAGNÒSTIC PER LA IMATGE

¿Qué es la Resonancia Magnética (RM)?

• Es una de las técnicas de diagnóstico por la imagen más modernas e inocuas. Mediante un potente imán y ondas de radio se generan imágenes del cuerpo humano.
• No utiliza Rayos X ni elementos radioactivos.
• No tiene efectos nocivos demostrados.
• Durante el estudio de RM, el médico y el técnico de la sala de control le hablarán y le controlarán mediante un monitor. Dispone de un avisador dentro del aparato por si necesita avisar al personal. Durante el procedimiento, el personal velará al máximo por su confort.

Precauciones

• Debe informarse sobre la necesidad o no de estar en ayunas. Especialmente si es la RM de un recién nacido o niño (por si fuera necesario sedarlo) o en los adultos que se hagan una RM abdominal.
• Comunique al personal sanitario si sufre alergias conocidas.
• Comunique al personal sanitario si es portador de objetos metálicos o electrónicos.
• Entre en la sala sin objetos metálicos.
• Para concretar el diagnóstico puede ser necesario administrar contraste endovenoso. En este caso le informarán previamente.
• Aporte la máxima información clínica de la que disponga, así como otras pruebas que le hayan hecho (Rx, TC o RM, sobre todo si se han realizado en otros centros).

Marcapasos y aparatos electrónicos

• Dado el riesgo de lesión y de mal funcionamiento del propio aparato, no se puede entrar en la sala con marcapasos cardiaco, estimuladores electrónicos o determinadas prótesis.
• Antes de entrar en la sala debe notificar al personal si es portador de aparatos electrónicos y se valorará la compatibilidad con la máquina de resonancia.

Embarazo

• A pesar de que no se han demostrado efectos nocivos de la RM sobre el feto, es recomendable que se notifique si la paciente está embarazada. En ciertas ocasiones se puede valorar clínicamente la idoneidad del estudio.

Mitjà de Contrast amb Gadolini

• En determinades ocasions és necessària l'administració d'un mitjà de contrast que permetrà arribar a un diagnòstic més concloent.

Què es el contrast?

• És un material (metall pesat) que en algunes patologies permet obtenir resultats més satisfactoris de l'RM, i així detectar de forma més adient certes lesions o patologies.
• S'administra en forma de líquid injectat per la vena.
• En determinades ocasions l'administració de Gadolini pot produir reaccions adverses lleus (cefalea, nàusees,...) i en casos molt poc freqüents reaccions greus.
• En casos reportats en pacients amb insuficiència renal greu, trasplantament hepàtic i malalties terminals s'ha descrit l'aparició d'una malaltia, la Fibrosi Sistèmica Nefrogènica. Aquesta malaltia té un ampli espectre de presentacions i pot ser invalidant.

Abans de la prova

• En cas de patir insuficiència renal greu, ser portador o estar en llista d'espera de trasplantament renal o hepàtic s'ha de comunicar, per tal que en funció del risc/benefici, antecedents i dades de la funció renal es decideixi la idoneïtat d'administrar contrast.
• En cas de reacció al·lèrgica prèvia comuniqui-ho, de forma que es puguin prendre les mesures adients.
• En cas de lactància es recomana suspendre la mateixa durant 24h un cop administrat el contrast.

Utilització de les imatges per a recerca

• En determinades ocasions les imatges diagnòstiques que se li realitzaran durant l'RM sol·licitada podrien fer-se servir amb finalitat docent, en la difusió del coneixement o en la recerca científica.
• El personal investigador de la Unitat d'RM podria necessitar algunes de les imatges per realitzar estudis que resultin en benefici dels pacients. En el seu cas es sol·licita permís pel projecte. En cas de que accedeixi la informació passaria a arxivar-se acomplint la normativa de confidencialitat de dades vigent.

Si una vegada llegida aquesta informació té alguna pregunta, no dubti en consultar al personal especialitzat de la Unitat de Ressonància Magnètica.

Medio de Contraste con Gadolinio

• En ocasiones es necesaria la administración de un medio de contraste que permitirá llegar a un diagnóstico más concluyente.

¿Qué es el contraste?

• Es un material (metal pesado) que en algunas patologías permite obtener resultados más satisfactorios de la RM, y así detectar de forma más adecuada ciertas lesiones o patologías.
• Se administra en forma de líquido inyectado por vena.
• En determinadas ocasiones, la administración de Gadolinio puede producir reacciones adversas leves (cefalea, náuseas,...) y en casos muy poco frecuentes, reacciones graves.
• En casos reportados en pacientes con insuficiencia renal grave, trasplante hepático y enfermedades terminales se ha descrito la aparición de Fibrosis Sistémica Nefrogénica. Esta enfermedad tiene un amplio espectro de presentaciones y puede ser invalidante.

Antes de la prueba

• En caso de sufrir insuficiencia renal grave, ser portador o estar en lista de espera de trasplante renal o hepático se debe comunicar, para que en función del riesgo/beneficio, antecedentes y datos de la función renal se decida la idoneidad de administrar contraste.
• En caso de reacción alérgica previa comuníquelo, de forma que se puedan tomar las medidas adecuadas.
• En caso de lactancia se recomienda suspender la misma durante 24 h un vez administrado el contraste.

Uso de las imágenes para investigación

• En determinadas ocasiones las imágenes diagnósticas que se le realizarán durante la RM solicitada podrían usarse con finalidad docente, en la difusión del conocimiento o en la investigación científica.
• El personal investigador de la Unidad de RM podría necesitar algunas imágenes para realizar estudios que resulten en beneficio de los pacientes. En su caso se solicita permiso para el proyecto. En caso de que acceda, la información pasaría a archivarse cumpliendo la normativa de confidencialidad de datos vigente.

Si una vez leída esta información tiene alguna pregunta, no dude en consultar al personal especializado de la Unidad de Resonancia Magnética.

ANNEX 8. Decompression of posterior fossa technique as described by Sahuquillo et al. in (48).

The operation is done with the patient in a prone position, with the neck in a slightly flexed position. 4 steps will be performed:

1. An extensive suboccipital craniectomy with a wide opening of the foramen magnum. Craniectomy has as superior limits, both transverse sinuses and extends laterally about 3 to 4 cm on each side of the midline. At this stage, a laminectomy low enough to expose the lowest level of the tonsils is also done. An extensive lateral bone removal at the level of the foramen magnum is performed.
2. The dura mater is opened while trying to preserve the arachnoid membrane intact. The dura is opened in a standard Y pattern. Preservation of the arachnoid membrane can be accomplished with the aid of the microscope or surgical loupes. A small opening in the dura is done first in the vertical limb of the dura incision; a blunt hook and a Penfield Number 4 dissector are used to separate the dura from the arachnoid. In cases in which the arachnoids are accidentally perforated, bipolar coagulation is used to try to seal the holes. No attempt is made to dissect the pia-arachnoid adherences found occasionally or to dissect or manipulate the tonsils.
3. The most important step in this procedure, is closing the dura watertight using a wide dural lyophilized allograft wide enough to allow a spacious posterior fossa to be reconstructed. Fibrin adhesive is used to completely seal the dural allograft.
4. Last, three to four tenting sutures are applied to the dural graft, passed through the muscles, and finally secured to the fascial plane. These sutures keep the dura mater away from the arachnoid membrane, preventing adherences to form and allowing an artificial cisterna magna to be formed behind and below the cerebellum.