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Postural control in Chiari I malformation: a paediatric trial protocol.

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Keywords: Chiari I malformation; paediatric neurosurgery; posturography.

ABSTRACT

Introduction: Chiari I malformation (CMI) is a rare disease characterized by the cerebellar tonsils descending at least 5 mm below the level of the foramen magnum. This can generate problems with cerebro-spinal fluid circulation and can also cause direct compression on the brainstem. It produces characteristic headaches, neurological impairment and syringomyelia. Surgery is the only available treatment, indicated when symptomatology is present. However, sometimes, patients complain about atypical symptoms suggestive of otolaryngological (ENT) involvement, which may be difficult for a neurosurgeon to explain. Our study aims to investigate the relationship between one of these atypical symptoms, i.e postural disorders, in a pediatric population thanks to a computerized dynamic posturography (Equitest®, NeuroCom, Clackamas, OR). In our knowledge, there are no previous published studies conducted on children with Chiari I malformation and utilizing dynamic posturography.

Methods: children aged 6 to 18 years old presenting with radiologically confirmed CMI and complaining of ENT symptoms will be included in the study. First, posturographic results will be described in the population study. Then, posturographic results will be compared between patients with and without indication for surgery. Finally, preoperative and postoperative results will be compared in the operated patient group.

Ethics and dissemination: this protocol was developed in agreement with the Clinical Research Delegation of Nancy University Hospital (protocol number 2019PI256-107), in accordance with the Commission Nationale de l'Informatique et des Libertés (National Commission on Informatics and Liberty). Our data treatment was in accordance with the Methodology of reference MR-004 specification for data policy.

Trial registration number

CLINICALTRIALS n° NCT04679792

Strengths and limitations of the study

- This is the first study which tries to evaluate postural control strategies in a pediatric population affected by Chiari I malformation, using dynamic posturography (Equitest®). This innovative study could allow for better understanding of some clinical aspects of this pathology, and could aid in the selection of patients for surgical intervention.
- Quantitative and qualitative data inherent to postural ability will be observed and collected, so as to make the research reproducible.
- The most important limitation of this study is the fact that we are accepting referrals from only one centre, which could slow inclusion rate and possibly delay results' publication.

INTRODUCTION

Chiari I malformation (CM1) is a disease characterized by cerebellar tonsillar descent below the level of the foramen magnum, into the vertebral canal. Once considered to be rare, it is now diagnosed more frequently due to the increasing utilization and sensitivity of neuroimaging, especially MRI.

Initially reported in the XII century by the Dutch physician and anatomist Nicholas Tulp (1593–1674) in its "Observationes Medicae" (1), its formal description has been attributed to Hans Chiari in 1896 (2,3). More than one hundred years later its firsts observations, CM1 is one of the most studied neurosurgical topics, with about four thousand scientific publications related to it. Despite that, some questions concerning this pathology remain unanswered and some aspects are not completely understood.

One of the questionable features which is sometimes disagreed upon in neurosurgery is the cause-and-effect relationship between some symptoms frequently reported by the patients but which are not historically attributed to the presence that of CM1 (4).

There are some cases of isolated neuro-otological manifestations such as nystagmus, dizziness and postural instability, which, as reported recently by Novegno (5), are atypical features of this malformation, and could create confusion in interpretation. To determine whether the malformation is symptomatic or not is of fundamental importance, because it constitutes the main argument for surgical intervention, which is the only possible treatment for this condition. When analyzing Chiari malformation from an anatomical point of view, however, it does not seem unreasonable to think that at times, patients may present with symptoms suggestive of ENT involvement (6). It is important to keep in mind, for example, that control of gait and balance (i.e. maintenance of equilibrium) requires somesthestic, visual and vestibular input. Many of the pathways and structures involved (medial longitudinal fasciculus, spinocerebellar tracts, vestibulospinal fasciculus, reticulospinal fasciculus, vestibular nuclei and nerves**)** are located in the brainstem in the craniocervical region, feeding both afferent and efferent collateral fibers to the cerebellum.

Literature about gait imbalance evaluation in CM1 patients is scarce, although ataxia and imbalance are frequently described (7–11). As a result, the patient is often referred to an otolaryngologist. Vestibular assessment (videonystagmography) is often helpful in these patients, as the presence of central pathology, along with normal caloric vestibular assessment, is very helpful at suggesting brainstem pathology while at the same time ruling out peripheral vestibular involvement (12).

Because of this, we decided to evaluate one of these uncommon aspects in children, i.e. postural instability, using Computerized Dynamic Posturography (CDP) (Equitest®, Neurocom, Clackamas, OR) at our institution (LAPEM laboratory, Brabois University Hospital in Nancy, France). To our knowledge, this is the only study using CDP in children with CM1.

Preliminary search and pilot study selection

Initial research was conducted following four main axes: typical symptoms of CM1 reported in neurosurgical reviews; ENT involvement in this pathology; developmental assessment of equilibrium control in children; dynamic posturography utilization in pediatric population.

Systematic review of the literature at the time of study design was performed using Index Medicus / PubMed electronic database, looking for typical symptoms of CM1 reported in neurosurgical articles. ENT studies reporting the interest of neuro-otological evaluation in Chiari I patients were then checked, and the following symptoms were individualized and underlined: nystagmus, dizziness, hearing loss and gait imbalance (12–27). Seven studies were selected to express the normal development of postural control in children (28–34), one of which underlines the feasibility and effectiveness of Equitest® use (32).

Posturographic method has been utilized in a study published in 2019 by Palamar et al. (35) to evaluate postural balance in CM1 patients. Static posturography (Tetrax® Interactive Postural Balance System (Sunlight Medical Ltd, IT) was used to assess postural control in 36 adult subjects, trying to find a correlation between the risk of fall (Fall Index) and degree of tonsillar ectopia, as well as presence of syringomyelia. The authors did not report significant results, but found a more elevated Fall Index in patients with more than 1 cm tonsillar ptosis.

STUDY OBJECTIVES

The aim of our study is to better elucidate the characteristics of body balance control in a pediatric population presenting a Chiari type I malformation; this evaluation will be performed utilizing CDP (Equitest®). To our knowledge, no similar previous studies have been published. The principle objective of this study is to describe posturographic results (before any surgery) in our population study.

We also wished to compare the CDP sensory organization test (SOT) patterns between patients with more severe cases of Chiari I malformation and less severe ones. The severity of the disease will be determined by surgical indication on the basis of actual neurosurgical criteria (described further); the decision for surgery will not be influenced by the current study.

In this study we also wished to compare evolution (i.e. preoperative versus 3-months postoperative) in (i) posturographic results, (ii) imaging results, (iii) symptomatology, (iv) sleep quality, (v) spinal balance (e.g. scoliosis) and (vi) behavior in the operated patient's group.

METHODS and MATERIALS

Trial design

This is a non-blinded, non-interventional, monocentric, multidisciplinary and prospective longitudinal clinical study. The ongoing results of the study will not influence surgical decisions.

Patients and Public Involvement

No patient was involved in the development of this study.

Population study

Inclusion criteria are:

- children aged from 6 to 18 years with CM1 confirmed by radiology.

This diagnosis was made by the presence of a caudal displacement of cerebellar tonsils of at least 5 mm under the foramen magnum (more precisely, under McRae's line, a radiographic line drawn on a midsagittal section of MRI that connects the anterior and posterior margins of the foramen magnum. This is traditionally used as a reference to determine foramen magnum level and is associated with problems of cerebrospinal fluid circulation at the foramen magnum level, and also a possible brainstem compression.

Non-inclusion criteria are:

- Chiari malformation secondary to other complex pathology (e.g. craniostenosis, severe craniocervical malformation, intracranial hypertension, posterior fossa tumor);
- inability to stand on the CDP platform, due to severe concomitant cerebral pathology or cerebral palsy, severe behavioral troubles, severe visual impairment, or associated orthopedic pathologies);
- preexisting vestibular pathology;
- refusal of parent to allow use of the indexed personal data.

Children who present pathologies or trouble listed in the above mentioned criteria cannot be included in the study because they carry factors that could interfere with posturographic results, thus making interpretation not available.

Study setting

At our institution, newly diagnosed CM1patients usually benefit from neurosurgical evaluation.

Patients will be recruited from a consult in a neurosurgical clinic, and will be completely evaluated by usual practice. This means that they will benefit from:

- complete clinical evaluation and precise anamnesis,
- medullary MRI, to check for syringomyelia,
- polysomnographic recording, to look for sleep apneas syndrome.

The clinical assessment and anamnesis will be recorded in a survey, ensuring that no valuable information is missed.

Patients who present symptoms like dizziness, nystagmus, gait impairment, motion sickness, malaises and atypical migraines which cannot be attributed to their CM1 will be referred for ENT assessment.

Group definition

Patients will be divided into two groups:

- patients who will benefit from surgical intervention,
- patients in whom there is no indication for surgery (these children will be followed until adulthood to check for CM1 modification over time).

Choice of comparators

Partition of the patients in the two groups will be made following standard neurosurgical selection criteria for surgery. The decision of surgical intervention is supported by the following examinations:

(i) anamnestic and clinical elements, (ii) cerebral and medullary MRI and (iii) polysomnography. A decision making flow chart is illustrated in Figure 1.

The criteria which lead neurosurgeon to decide for surgical intervention are represented by the presence of at least one of the following aspects:

- characteristic symptomatology (most of all, exertional headaches, usually occipito-cervical, but also of frontal location; presence of symptoms of brainstem compression),
- syringomyelia,
- central sleep apnea.

Investigation

ENT assessment will be carried out in both groups (surgical and non-surgical) presenting with symptoms requiring specialist examination.

This evaluation will be made up of neuro-otological assessment, and also clinical vestibular assessment, if deemed necessary.

The clinical neuro-otological assessment aims at detecting and discriminating cerebellar and vestibular syndrome, identifying segmental or axial deviations, and ruling out confounding associated factors of patients' symptoms.

A cerebellar syndrome is looked for by the finger to nose test, alternating hand movements (dysdiadochokinesia) and by the increase of the sustentation polygon in the Fukuda stepping maneuver (cerebellar ataxia).

Concerning the vestibular syndrome, the consequences of a vestibular lesion can be appreciated thanks to the evaluation of the following anatomic pathway: the vestibulo-ocular pathway (trouble being expressed by the presence of nystagmus), the vestibulo-spinal pathway (which lesion can produce instability), the vegetative pathway (linked to nausea and vomiting) and the perceptual (vestibulo-cortical) pathway (which lesion may produce vertigo).

The assessment checks for a possible nystagmus in different plans. Moreover, without moving the head, the child fixates with his/her eyes a target moving in a regular sinusoidal movement from left to right and from right to left (smooth or saccadic pursuit). Nystagmus is the most common and is usually due to peripheral or central vestibular impairment.

In addition to a neuro-otological assessment, other factors evaluated included vergence insufficiency, refraction disorders (in particular astigmatism), not carried visual correction. It is sometimes necessary to ask for a complementary ophthalmological or orthoptic assessment. The amount of time spent on computer screens and videogames are also taken into account.

Vertigo or dizziness can have multiple causes in the same patient.

The diagnosis of a type of vertigo relies mainly upon the history taken from the patient, including family history, and the clinical examination; the presence of dizziness, gait instability, history of head trauma and falls, headache, drugs intake, motion sickness susceptibility are also noted.

If vertigos are present, they have to be precisely described (starting date, number, frequency, duration, intensity) in order to determine an eventual evolutionary pattern: relation time / disability, iterative vertigo (periodic or paroxystic), chronic vertigo.

The following triggers are sought: head versus trunk movement, movement of the head in space, quick standing, stressing situation (cardio-vascular origin).

False vertigos are eliminated (illusion of movement not related to balance control pathways, fear of heights…)(36).

Vertigo or unsteadiness can be associated to sensorineural and conductive hearing loss. Concerning the later, otitis media and previous ear surgery are noted. Tinnitus are also addressed.

Otoscopic examination preceded tympanometric curves and acoustic reflex test recordings (Interacoustics, Middelfart, Denmark) and determining hearing thresholds (pure-tone air and bone-conduction thresholds) in tone audiometry (from 250 Hz to 8000 Hz) and intelligibility in speech tests (Interacoustics).

After such a clinical examination, (CDP) will be carried out to determine balance control performances.

Computerized dynamic posturography (Equitest®, NeuroCom, Clackamas, OR) assesses global balance performance and relative weight of each sensory information (visual, vestibular, and somatosensory) involved in balance control. Equitest balance system is composed by a dual platform which consists of two footplates connected by a pin joint and supported by four symmetric force transducers (strain gauges), mounted on a supporting center plate, and by a fifth transducer bracketed to the center plate directly beneath the pin joint. The center transducer measures shear forces along the Y axis, in the plane parallel to the floor, while the other transducers measure vertical forces applied to the dual platform. Force data are sampled at 100 Hz and stored on a PC using a 12-bit A/D converter. The computer calculates the center of foot pressure (CoP) and the vertical component of the center of gravity (CoG), using the subject's height entered by the operator. When a subject stands with ankles centered over the stripe on the dual platform, with feet an equal distance laterally from the center line (Y axis), CoG is located directly above the intersection of the X and Y axes (position called electrical zero position, which serves as a reference point for the calculation of sway angles). The program uses a small angle approximation to arcsin x, which is accurate to 0.5% in the range of angles encountered.

The sensory organization test (SOT) consists of three 20-sec trials under six different sensory conditions in which the surface and/or visual surround are systematically manipulated. Accordingly, the movable platform and visual surrounding are used to manipulate sensory inputs during the SOT (Table 1) (37–40).

Postural control test		
Name	Situation	Sensory consequences
Condition 1	Fixed support, eyes open	-
Condition 2	Fixed support, eyes closed	Vision absent
Condition 3	Fixed support, SR surround	Altered vision
Condition 4	SR support, eyes open	Altered proprioception
Condition 5	SR support, yes closed	Vision absent, altered proprioception
Condition 6	SR support, SR surround	Altered vision and proprioception

Table 1: Computerized dynamic posturography. Sensory organization test (Equitest®, NeuroCom, Clackamas, OR). Determination of the six conditions. SR, sway-referenced (38–40).

Examination in eyes closed situations (conditions 2 and 5) may be get more complex by 30° rhythmic flexo-extension movements of the head, to better evaluate vestibular function and cervical muscles somatosensory component (see below); this might be of particular interest in patients with Chiari malformation, pathology that involved cervical muscle's function. To protect against falls, patients wear a safety harness connected to the ceiling an operator stood within reaching distance. An equilibrium score (ES) is calculated by comparing the subject's anterior-posterior sway during each 20 s SOT trial to the maximal theoretical sway limits of stability, which is based on the individual's height and size of the base of support. It represents an angle (8.0 anteriorly and 4.0 posteriorly) at which the subject can lean in any direction before the center of gravity would move beyond a point that allows him/her to remain upright (i.e., point of falling). The following formula is used to calculate the ES:

$$\text{Equilibrium} = 12.5° - (\theta\text{max} - \theta\text{min}) / 12.5° \times 100$$

where θmax indicates the greatest antero-posterior CoG sway angle displayed by the subject, while θmin indicates the lowest antero-posterior CoG sway angle. Lower sways lead to a higher ES, indicating a better balance control performance (a score of 100 represents no sway, while 0 indicates sway that exceeds the limit of stability, resulting in a fall). Table 2 shows CES and sensory ratios calculation's method.

Name	Equation	Significance
Composite score	[C1 + C2 + 3 (C3 + C4 + C5 + C6)] / 14	Evaluate global balance performance. High score being representative of good postural control
Somatosensory ratio	C2 / C1	Ability somatosensory input to maintain balance (even when visual cues are removed). Low score: poor use of somatosensory references
Visual ratio	C4 / C1	Ability to use visual input to maintain balance (even when somatosensory cues are altered). Low scores: poor use of visual references
Vestibular ratio	C5 / C1	Ability to use vestibular input system to maintain balance (even when visual cues are removed and somatosensory cues are altered). Low scores: poor use of vestibular cues or vestibular cues unavailable
Visual preference ratio	C3 + C6 / C2 + C5	Degree to which patient relies on visual information to maintain balance (correct/incorrect information). Low scores: reliance on visual cues even inaccurate

Table 2: Computerized dynamic posturography. Sensory organization test (Equitest®, NeuroCom, Clackamas, OR). Significance of composite score and sensory ratios. SR, sway-referenced.

Posturography is also useful in evaluation of the patient with multiple pathologies affecting several components of the sensorimotor chain (inner ear, vision, and somesthetic). Evaluation of some of these patients is often made more complicated by the fact that pathology is often partially compensated for, to the point where symptoms and abnormalities are often minimized (41).

Association between Chiari malformation and scoliosis is well known, scoliosis, which can be a factor in balance impairment (42) and altered oculomotor functions (43). For this reason, these factors will also be taken into account in the assessment.

Outcomes

Primary outcome

The Composite Equilibrium Score (CES), which evaluates global balance performance, will be our primary endpoint, along with the reported visual, somesthetic and vestibular components.

We also will carry out the following evaluations:

- A Head Shake Sensory Organization Test (details of this assessment are outlined in the literature (44–47). consisting during 20 sec of repetitive forward and backward flexions of the head, these head tilts provocative condition of 30° in the pitch plane (cervical flexion / extension) at 0.33 Hz stimulating the cervical proprioception and muscles, as well as the two inner ears. This sensory stimulation was tested in eyes closed condition, both stable (during condition 2) and sway-referenced platform (during condition 5). We feel it important to assess these parameters as these patients may present with cervical pain and muscle impairment.
- Lateral displacements of the center of gravity, used to quantify the postural sway in the medial-laterally plane.

We also wish to evaluate postural strategies that will be adopted. As outlined in the literature, there are two strategies; a bottom-up regulation model, where the body is oscillating like an inverted pendulum (“ankle strategy”), and a top down strategy (a pattern favoring visual preference involved (“hip strategy”). According to this model, postural control in the sagittal plane is by default exerted around the ankle joint and then (if the postural challenge increases) by the hip joint (48–50)

Secondary outcome

The secondary outcomes are the following:

- Efficacy of surgical intervention to restore cerebrospinal fluid circulation at foramen magnum level.

A single observer (IS) will be in charge of assessing it by comparing pre-operative and 3 months’ postoperative MRI, using a three points scale: 0 = any modification appreciated; 1 = improved tonsillar ptosis; 2 = resolved tonsillar ptosis with reappearance of a cisterna magna.

- Effectiveness of surgical intervention on an eventually preexisting syringomyelia

Improvement will be considered when the cavity’s size (maximum anteroposterior diameter) is reduced by at least 30% between pre-operative and 3 month’s postoperative medullary MRI. Stability will be considered in case of cavity’s size reduction from 0% to less than 30%, while any degree of increase in size will be considered as aggravation.

- Efficacy of surgical intervention to improve sleep quality

In case of preexisting apneas syndrome before surgery, evolution in the ratio between total and partial respiratory interruption (i.e. apnea/hypopnea index) between pre-operative and 3 month's postoperative polysomnography will be considered. A reduction of at least 50% in this ratio will be considered as improvement.

- Effectiveness of surgical intervention to arrest vertebral imbalance (scoliosis)

In case of preexisting vertebral imbalance, corresponding to a Cobb's angle over 10°, none or minimal Cobb's angle change (< 5°) of the preexisting scoliosis will be considered as a favorable outcome.

- Influence of surgery on patient's behavior (Yes/No)

Based on parents' feelings at least 3 months after surgical intervention, change in patient's behavior (Yes/No) will be assessed at a routine follow up.

Timeline

Patients' data are collecting from September 2020 to March 2022

Data collection method

The data are collected by principal investigator in an electronic and an anonymous database, password –protected and stored on the principal investigator's professional computer.

Data collection will be carried out in accordance with the Commission Nationale de l'Informatique et des Libertés.

Patient's families give their oral consent to anonymous treatment of data.

Statistical methods

Primary outcome

Data will be described through counts and percentages for qualitative variables and means standard deviation or median and extreme values for quantitative variables (depending on the nature of the distribution).

Secondary outcomes

Intergroup comparison of posturographic results will be performed using Student's t-test or Mann–Whitney U test depending on the nature of the distribution. Comparison between "Before surgery" and "After surgery results" will be performed using Mc Nemar test or symmetry test categorical variables and Student's test or Wilcoxon's test on paired series for continuous variables.

Data monitoring: formal committee and interim analysis

No data monitoring committee has been appointed, due to the absence of recruitment problem and inclusion criteria based on neurosurgical arguments.

An interim analysis of outcomes has not been planned, due to the prompt interpretation of investigation's results.

Adverse effects

No adverse effect of the proposed investigation is conceivable.

Auditing

This study's protocol is under control of the institution's Delegation to Clinical Research and innovation (DRCI), who managed ethical issues and research quality; patients' data are checked and elaborated by Methodology, Data management and Statistic department (UMDS).

Access to data

The first author (IS) is the only person who has knowledge of the identity of the recruited patients and the results of patients' investigations. Data are collected in a protected computerized database only accessible to first author.

Pre-registration

This protocol has been registered at https://clinicaltrials.gov, identifier CLINICALTRIALS NCT04679792. Log in required to access records.

Dissemination policy

Trial results

The study's results will be submitted for publication in a peer-reviewed journal, conforming to the definition of the outcome presented in this protocol.

Sponsor

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University of Lorraine, 54511 Vandoeuvre-lès-Nancy, France

Steering committee

It is composed by the main authors of this report, headed by Professor Philippe Perrin, principal investigator of the study.

Trial promotion and funding

This study has been selected as the award winner of "Neurosphynx 2021 call for project". The NeuroSphinx branch coordinates the investigators concerned with rare pelvic and medullary malformations with sphincter damage. The diseases and malformations concerned are those which affect the marrow and the caudal pole. NeuroSphinx brings together 3 Rare Disease Reference Centers, of which C - MAVEM is the specific one who organizes the caregiving of syringomyelia, Chiari and

vertebral-medullary malformations. It promotes patients-health givers communication as well as research advances.

Thanks to this award, we have received financial support from Neurosphynx in order to face bureaucratic expenses (publishing, platform maintenance...); otherwise, this is a no-cost study without extra costs.

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Footnotes

- **Collaborators** Dr Art Mallinson
- **Contributors** IS, OK and PP have conceived and designed the study; IS, OK, PP and AJ manage medical aspects of the patients; IS has written the paper while OK, PP and RT have participated in writing the paper; AP ensure the technical aspect of the posturography; RT cares about statistical analysis.
- **Funding** The project won a financial award from Neuroshynx, who nationally coordinates the Reference Center for Chiari malformation and Rare vertebra-medullary diseases.
- **Competing interests** The authors declare that there is not conflict of interest.

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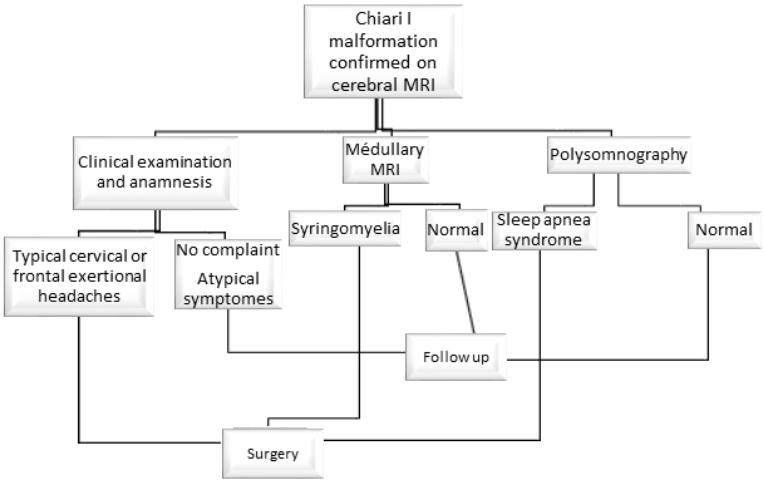
FIGURES' LEGEND

Fig. 1 – Decision making flow chart for new diagnosed-case of Chiari I malformation.

Fig. 2 – Posturographic results (Equitest®, NeuroCom, Clackamas, OR) in one of operated patients. Sensory Organization Test: the composite equilibrium score increased from 68 before surgery (Fig. 2 a) to 77 after surgery (Fig. 2b). Somatosensory (SOM), visual (VIS) and vestibular (VEST) ratios increased respectively from 90 to 96, 85 to 91 and 51 to 60 before to after the surgery.



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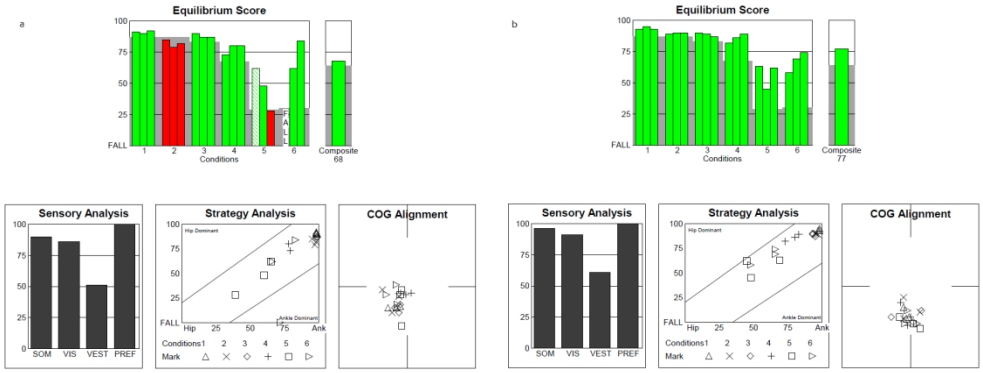
532x361mm (38 x 38 DPI)



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Postural control in Chiari I malformation: a paediatric prospective, observational cohort. Potential role of posturography for surgical indication.

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Postural control in Chiari I malformation: a paediatric prospective, observational cohort. Potential role of posturography for surgical indication.

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ABSTRACT

Introduction: Chiari I malformation (CM1) is an anatomical abnormality characterized by the cerebellar tonsils descending at least 5 mm below the level of the foramen magnum. CM1 can cause obstruction of cerebrospinal fluid (CSF) circulation as well as direct compression on the brainstem, thus causing typical consequences (syringomyelia), and typical clinical features (characteristic headaches and neurological impairment). Surgery is the only available treatment, indicated when symptomatology is present. However, sometimes, patients have atypical complaints, which are often suggestive of otolaryngological (ENT) involvement. This may be difficult for a neurosurgeon to explain. Our study aims to investigate the relationship between one of these atypical symptoms, e.g. postural instability, in a paediatric population using a Computerized Dynamic Posturography platform (Equitest®, NeuroCom, Clackamas, OR). To our knowledge, there are no previously published studies carried out on children with Chiari I malformation, utilizing dynamic posturography.

Methods and analysis: forty-five children aged 6 to 18 years old presenting with radiologically confirmed CM1 and presenting ENT clinical complaints will be included in the study for a duration of 3 years. As primary endpoint, posturographic results will be described in the population study. Secondly, posturographic results will be compared between patients with and without indication for surgery. Finally, pre- and postoperative posturographic results, as well as CSF circulation quality at foramen magnum level, syringomyelia, sleep apnea syndrome, scoliosis and behavior will be compared in the operated patient group.

Ethics and dissemination: this protocol was developed in agreement with the Clinical Research Delegation of Nancy University Hospital, in accordance with the National Commission on Informatics and Liberties (Commission Nationale de l'Informatique et des Libertés) (protocol number 2019PI256-107). Our data treatment was in accordance with the Methodology of reference MR-004 specification for data policy.

Protocol registration number

CLINICALTRIALS n° NCT04679792 (17th December 2020).

Strengths and limitations of the study

- This is the first study which tries to evaluate postural control strategies in a paediatric population affected by Chiari I malformation, using dynamic posturography (Equitest®).
- It is a prospective, observational, monocentric study which aims to compare operated vs non operated patients with Chiari I malformation.
- Quantitative and qualitative data inherent to postural ability will be observed and collected, so as to make the research reproducible.
- This protocol could represent the starting point for a wider, multicenter study.

INTRODUCTION

Chiari I malformation (CM1) is a structural abnormality characterized by cerebellar tonsillar descent of at least 5 mm below the level of the foramen magnum (1), into the vertebral canal. Once considered to be rare, it is now quite often diagnosed incidentally due to the increasing utilization and sensitivity of neuroimaging, especially MRI. Although the true prevalence in the general population is difficult to establish, the imaging incidence in children younger than 18 years has been reported from 0.4 to 3.6% (2,3)

Initially reported in the XII century by Nicholas Tulp in its "Observationes Medicae" (4), its formal description has been attributed to Hans Chiari in 1896 (5,6). Despite CM1 is actually one of the most studied neurosurgical topics, some aspects concerning this malformation (i.e. pathogenesis, evolution and treatment) remain controversial (2), so that different studies are in progress with the aim of clarifying the natural history and best management of CM1 (7).

While 14% to 21% of people remain asymptomatic (8), most patients present with a constellation of clinical features which are diverse and which can impair their quality of life. The most typical symptom attributed to CM1 is pain; this paroxysmal symptom is usually localized to the occipital-cervical region and it is normally associated with a Valsalva maneuver such as coughing, laughing or sneezing. Other neurological symptoms or signs are related to brainstem or cranial nerve compression or distortion, and are represented by long tract sensitive-motor deficit, hyperreflexia, Babinski sign, sleep apnea syndrome and, less commonly, vocal cord paralysis, palatal weakness and dysarthria (9). If syringomyelia is associated, as in 45-75% of patients (10,11), one can also see a typical clinical expression such as distal-to-proximal weakness of the upper limbs with a cape-like suspended sensory loss. Less commonly, cerebellar syndrome with nystagmus, dysarthric speech and ataxia may be present (9).

Given the fact that the clinical presentation of CM1 is highly variable, and often accompanied by less than clear subjective somatic complaints (12), in everyday practice it is sometimes difficult to state whether CM1 is really symptomatic or not. Some neuro-otological manifestations (such as nystagmus, dizziness and imbalance) are reported in CM1, but these features have been described as "atypical" (13), thus creating confusion in interpretation.

Whether the malformation is symptomatic or not is of fundamental importance to determine if the patient is a candidate for surgical intervention; surgery is the only possible treatment for this abnormality.

When analyzing CM1 from an anatomical point of view, however, it is not unreasonable to think that patients may present with symptoms and signs suggestive of otolaryngological (ENT) involvement (14). As a matter of fact, it is important to keep in mind that many of the pathways and structures responsible for balance and gait control (i.e. medial longitudinal fasciculus, spinocerebellar tracts, vestibulospinal fasciculus, reticulospinal fasciculus, vestibular nuclei and nerves) are located in the brainstem in the craniocervical region, feeding both afferent and efferent collateral fibers to the cerebellum.

Moreover, ataxia is rarely found on neurological standard clinical examination in CM1 patients and its formal characterization is difficult in the paediatric population.

For these reasons, we feel that detailed clinical evaluation, including objective testing might be advantageous in this population. Literature about instrumental imbalance evaluation in CM1 patients is scarce, although ataxia and dizziness are frequently described (9,15–18). We decided to evaluate one of these uncommon aspects in children, i.e. imbalance, using Computerized Dynamic Posturography (CDP) (Equitest®, Neurocom, Clackamas, OR) at our institution (LAPEM laboratory, Brabois University Hospital in Nancy, France). To our knowledge, this is the only study using CDP in children with CM1.

Preliminary search and pilot study selection

Initial research was conducted following four main axes:

- typical symptoms of CM1 reported in neurosurgical reviews,
- ENT involvement in this pathology,
- developmental assessment of equilibrium control in children,
- dynamic posturography recordings in pediatric population.

Systematic review of the literature at the time of study design was performed using an Index Medicus and PubMed electronic database, looking for typical symptoms of CM1 reported in neurosurgical articles. ENT studies reporting the interest of neuro-otological evaluation in Chiari I patients were then checked, and the following clinical features were individualized and underlined: nystagmus, dizziness, hearing loss and gait imbalance (19–34). Seven studies were selected to express the normal development of postural control in children (35–41), two of which underline the feasibility and effectiveness of Equitest® (39,42).

Posturographic evaluation in CM1 patients has been utilized in a study published in 2019 by Palamar et al. (43). Static posturography (Tetrax® Interactive Postural Balance System (Sunlight Medical Ltd, IT) was used in 36 adult subjects, trying to find a correlation between the risk of fall (Fall Index) and degree of tonsillar ectopia, as well as presence of syringomyelia. The authors did not report significant results, but found a more elevated Fall Index in patients with more than 1 cm tonsillar ptosis.

Study objectives

The aim of our research is to study and examine the characteristics of balance control in a paediatric population presenting with CM1. This evaluation will be performed utilizing CDP (Equitest®). To our knowledge, no similar previous studies have been published.

We also wished to compare the CDP sensory organization test (SOT) patterns between patients with surgical cases of CM1 and non-surgical ones. Surgical indication, determined on the basis of actual neurosurgical criteria, will not be influenced by the results of this study.

Our study will also compare preoperative versus 3-months postoperative assessments with regard to (i) posturographic results, (ii) imaging results, (iii) symptomatology, (iv) sleep quality, (v) spinal balance (e.g. scoliosis) and (vi) behavior in the group of operated patients.

METHODS and ANALYSIS

Protocol design

This is a non-blinded, non-interventional, monocentric, multidisciplinary and prospective, observational, longitudinal clinical study. The ongoing results of the study will not influence surgical decisions.

Patients and Public Involvement

No patient was involved in the development of this study.

Population study

A total of 45 patients will be enrolled in the study for a duration of 3 years.

Inclusion criteria are:

- children aged from 6 to 18 years with CM1 confirmed by radiology,
- children presenting clinical features suggesting ENT involvement (dizziness, nystagmus, gait impairment, motion sickness, malaises and atypical migraines which cannot be directly attributed to the CM1),
- children whose parents/guardians agreed to participation in the study, after being supplied detailed oral and written information.

Diagnosis of CM1 was made by the presence of a caudal displacement of cerebellar tonsils of at least 5 mm under the foramen magnum (more precisely, under McRae's line, a radiographic line drawn on a midsagittal section of MRI that connects the anterior and posterior margins of the foramen magnum). This is traditionally used as a reference to determine foramen magnum level (1) and is associated with problems of cerebrospinal fluid circulation at the foramen magnum level, and also a possible brainstem compression.

Non-inclusion criteria are:

- Chiari malformation secondary to other complex pathology (e.g. craniostenosis, severe craniocervical malformation, intracranial hypertension, posterior fossa tumor);
- inability to stand on the CDP platform, due to cerebral palsy, severe behavioral troubles, severe visual impairment, or associated orthopedic pathologies;
- preexisting vestibular pathology;
- refusal of parent to allow use of the indexed personal data.

Study setting

Newly diagnosed CM1 patients recruited at Nancy University Regional Hospital (France) initially undergo neurosurgical evaluation to perform a complete clinical evaluation and precise anamnesis, that will be recorded in a survey, ensuring that no valuable information is missed.

Afterward, patients are systematically sent to perform these two fundamental exams:

- medullary MRI, to check for syringomyelia,
- polysomnographic recording, to look for sleep apnea syndrome.

Patients who present clinical pictures such as dizziness, nystagmus, gait impairment, disabling motion sickness, malaise and atypical migraines which cannot be attributed to their CM1 will be referred for ENT assessment, including neuro-otological examination and CDP.

Group definition

Patients will be allocated into two groups:

- patients who will benefit from surgical intervention (who will be followed up for several years after the intervention),
- patients in whom there is no indication for surgery (who will be followed until adulthood to check for CM1 modification over time).

Choice of comparators

Partition of the patients into the two groups will be made following standard neurosurgical selection criteria for surgery. The decision for surgical intervention is supported by the following examinations: (i) anamnestic and clinical elements, (ii) cerebral and medullary MRI and (iii) polysomnography. A decision making flow chart is illustrated in Figure 1.

The criteria which lead the neurosurgeon to decide on surgical intervention are represented by the presence of at least one of the following aspects:

- characteristic symptomatology (most of all, exertional headaches, usually occipito-cervical, but also of frontal location; presence of symptoms of brainstem compression),
- syringomyelia,
- central sleep apnea.

Investigations

ENT assessment will be carried out in both surgical and non-surgical groups presenting with symptoms requiring specialist examination, as mentioned above. It will consist of a neuro-otological examination and clinical vestibular assessment, if deemed necessary.

The aims of the neuro-otological examination are to detect and differentiate cerebellar and vestibular signs, identify segmental or axial deviations, and rule out confounding associated factors.

A cerebellar syndrome is recognized by the finger to nose test (dysmetria), alternating hand movements (dysdiadochokinesis) and by the increase of the polygon in the Fukuda stepping test (cerebellar ataxia).

With regards to a vestibular syndrome, the consequences of a vestibular lesion can be appreciated by evaluating the vestibulo-ocular pathway (evidenced by the presence of nystagmus), the vestibulo-spinal pathway (which can produce instability), the vegetative pathway (linked to nausea and vomiting) and the perceptual (vestibulo-cortical) pathway (which can produce true vertigo). Videonystagmography, along with normal caloric vestibular assessment, is very helpful at suggesting brainstem pathology and ruling out peripheral vestibular involvement (21).

Patients are also evaluated for the presence of nystagmus, which is usually due to peripheral or central vestibular impairment.

Other evaluated factors included vergence insufficiency, refraction disorders, or other visual correction. It is sometimes necessary to ask for a complementary ophthalmological or orthoptic assessment.

Vertigo or dizziness can have multiple causes in the same patient and will be accurately assessed. The diagnosis of the type of vertigo relies mainly upon the history taken from the patient and the clinical examination. Any history of head trauma and falls, headache, drug intake, and motion sickness susceptibility is noted. If spells of true vertigo are occurring, they need to be precisely described (starting date, number, frequency, duration, intensity) in order to determine an eventual evolutionary pattern. The following triggers are sought: head versus trunk movement, movement of the head in space, quick standing, stressing situations (cardio-vascular origin). So called “false vertigo” should be eliminated (44). Vertigo or unsteadiness can be associated with sensorineural and conductive hearing loss. Otitis media and previous ear surgery are noted. Complaints of tinnitus should also be addressed.

Otoscopic examination will also be carried out, with tympanometry and acoustic reflex test recordings (Interacoustics, Middelfart, Denmark) and determining hearing thresholds (pure-tone air and bone-conduction thresholds) in tone audiometry (from 250 Hz to 8000 Hz) and intelligibility in speech tests (Interacoustics).

After that, CDP will be carried out to determine balance control performances.

CDP (Equitest®, NeuroCom, Clackamas, OR) assesses global balance performance and relative weight of sensory information (visual, vestibular, and somatosensory) involved in balance control. The Equitest balance system consists of a dual platform with two footplates connected by a pin join. The footoplates are supported by five force transducers. The computer calculates the center of foot

pressure (CoP) and the vertical component of the center of gravity (CoG), using the subject's height entered by the operator. When a subject stands with ankles centered over the stripe on the dual platform, with feet an equal distance laterally from the center line, he is in the a position called "electrical zero position", which serves as a reference point for the calculation of sway angles.

The sensory organization test (SOT) consists of three 20-sec trials under six different sensory conditions in which the surface and/or visual surround (i.e. sensory inputs) are systematically manipulated (so-called "sway referencing"). (Table 1) (43–46).

Postural control test		
Name	Situation	Sensory consequences
Condition 1	Fixed support, eyes open	-
Condition 2	Fixed support, eyes closed	Vision absent
Condition 3	Fixed support, SR surround	Altered vision
Condition 4	SR support, eyes open	Altered proprioception
Condition 5	SR support, eyes closed	Vision absent, altered proprioception
Condition 6	SR support SR surround	Altered vision and proprioception

Table 1: Computerized dynamic posturography. Sensory organization test (Equitest®, NeuroCom, Clackamas, OR). Determination of the six conditions. SR, sway-referenced (42,46,47).

Examination in eyes closed situations (conditions 2 and 5) may be made more complex by 30° rhythmic flexo-extension movements of the head, to better evaluate the somatosensory component of vestibular function and cervical muscles (see below). This might be of particular interest in patients with Chiari malformation. To protect against falls, patients wear a safety harness connected to the ceiling and an operator stands within reaching distance. An equilibrium score (ES) is calculated by comparing the subject's anterior-posterior sway during each 20 s SOT trial to the maximal theoretical sway limits of stability, which is based on the individual's height and size of the base of support. It represents an angle (8.0 anteriorly and 4.5 posteriorly) at which the subject can lean in any direction before the center of gravity would move beyond a point that allows him/her to remain upright (i.e., point of falling). The following formula is used to calculate the ES:

$$\text{Equilibrium} = 12.5° - (\theta\text{max} - \theta\text{min}) / 12.5° \times 100$$

where θmax indicates the greatest antero-posterior CoG sway angle, θmin indicates the lowest antero-posterior CoG sway angle. Lower sways lead to a higher ES, indicating a better balance control performance (a score of 100 represents no sway, while 0 indicates sway that exceeds the limit of stability, resulting in a fall). Table 2 shows CES and sensory ratios calculation's method.

Name	Equation	Significance

Composite score	[C1 + C2 + 3 (C3 + C4 + C5 + C6)] / 14	Evaluate global balance performance. A low score represents poor postural control
Somatosensory ratio	C2 / C1	Ability to use somatosensory input to maintain balance (even when visual cues are removed). A low score suggests poor use of somatosensory references
Visual ratio	C4 / C1	Ability to use visual input to maintain balance (even when somatosensory cues are altered). A low score suggests poor use of visual references
Vestibular ratio	C5 / C1	Ability to use vestibular input system to maintain balance (even when visual cues are removed and somatosensory cues are altered). a low score suggests poor use of vestibular cues or that vestibular information is unavailable
Visual preference ratio	C3 + C6 / C2 + C5	Degree to which patient relies on visual information to maintain balance (correct/incorrect information). A low score suggests reliance on visual cues even when they are inaccurate

Table 2: Computerized dynamic posturography. Sensory organization test (Equitest®, NeuroCom, Clackamas, OR). Significance of composite score and sensory ratios.

Posturography is also useful in evaluation of the patient with multiple pathologies affecting several components of the sensorimotor chain (inner ear, vision, and somesthetic). (48).

An example of CDP preoperative and postoperative results is illustrated in the Figure 2.

Association between Chiari malformation and scoliosis is well known; scoliosis can be a factor in balance impairment (49) and altered oculomotor functions (50). Accordingly, these factors will also be taken into account in the assessment.

Outcomes

Primary outcome

The Composite Equilibrium Score (CES) will be our primary endpoint, along with the reported visual, somesthetic and vestibular components.

We also will carry out the following evaluations:

- A Head Shake Sensory Organization Test (details of this assessment are outlined in the literature (51–54) consisting during 20 sec of repetitive forward and backward flexions of the head, these head tilts provocative condition of 30° in the pitch plane (cervical flexion / extension) at 0.33 Hz stimulating the cervical proprioception and muscles, as well as the two inner ears. This sensory stimulation was tested in eyes closed condition, both stable (during condition 2) and sway-referenced platform (during condition 5). We feel it important to assess these parameters as these patients may present with cervical pain and muscle impairment.
- Lateral displacements of the center of gravity, used to quantify the postural sway in the medial-laterally plane.

We also wish to evaluate postural strategies that will be adopted. As outlined in the literature, there are two strategies; a bottom-up regulation model, where the body is oscillating like an inverted pendulum ("ankle strategy"), and a top down strategy (a pattern favoring visual preference involved ("hip strategy"). According to this model, postural control in the sagittal plane is by default exerted around the ankle joint and then (if the postural challenge increases) by the hip joint (55–57)

Secondary outcome

The secondary outcomes are the following.

- CDP results comparison between surgical and not surgical patients,
- Efficacy of surgical intervention to restore cerebrospinal fluid circulation at foramen magnum level.

A single observer (IS) will be in charge of assessing the radiological assessments by comparing pre-operative and 3 months' postoperative MRI, using a three-point scale: 0 = any modification appreciated; 1 = improved tonsillar ptosis; 2 = resolved tonsillar ptosis with reappearance of a cisterna magna.

- Effectiveness of surgical intervention on a preexisting syringomyelia.

Improvement will be considered when the cavity's size (maximum anteroposterior diameter) is reduced by at least 30% between pre-operative and 3 month's postoperative medullary MRI. Stability will be considered in case of cavity's size reduction from 0% to less than 30%, while any degree of increase in size will be considered as aggravation.

- Efficacy of surgical intervention to improve sleep quality.

In case of preexisting apnea syndrome before surgery, evolution in the ratio between total and partial respiratory interruption (i.e. apnea/hypopnea index) between pre-operative and 3 month's postoperative polysomnography will be considered. A reduction of at least 50% in this ratio will be considered as improvement.

- Effectiveness of surgical intervention to arrest vertebral imbalance (scoliosis).

In case of preexisting vertebral imbalance, corresponding to a Cobb's angle over 10°, none or minimal Cobb's angle change (< 5°) of the preexisting scoliosis will be considered as a favorable outcome.

- Influence of surgery on patient's behavior (Yes/No).

Based on parents' feelings at least 3 months after surgical intervention, change in patient's behavior (Yes/No) will be assessed at a routine follow up.

Statistical methods

Primary outcome

Data will be analyzed with counts and percentages for qualitative variables and means standard deviation or median and extreme values for quantitative variables (depending on the nature of the distribution).

Secondary outcomes

Intergroup comparison of posturographic results will be performed using Student's t-test or Mann–Whitney U test depending on the nature of the distribution. Comparison between "Before surgery" and "After surgery results" will be performed using Mc Nemar test or symmetry test categorical variables and Student's test or Wilcoxon's test on paired series for continuous variables.

Data collection method

The data are collected by principal investigator in an electronic and anonymous database which is password protected and stored on the principal investigator's professional computer.

Data collection will be carried out in accordance with the National Commission on Informatics and Liberties (Commission Nationale de l'Informatique et des Libertés) policy.
During the study, the collection of data will be interrupted and the data previously collected will not be used if the person participating in the research objects to the use of their data.

Data monitoring: formal committee and interim analysis

No data monitoring committee has been appointed, due to the absence of recruitment problem and inclusion criteria based on neurosurgical arguments.

An interim analysis of outcomes has not been planned, due to the prompt interpretation of investigation's results.

Timeline

Patients' data are collecting from September 2020 to March 2023

Adverse effects

No adverse effect of the proposed investigation is conceivable.

Pre-registration

This protocol has been registered in ClinicalTrial.gov, identifier CLINICALTRIALS NCT04679792 (17th December 2020). Log in required to access records.

ETHICS AND DISSEMINATION

Approvals

This protocol has been approved by the Delegation for Clinical Research and Innovation (Délégation à la Recherche Clinique et à l'Innovation – DRCI) of the Nancy University Hospital, in accordance with the National Commission for Computing and Liberties (Commission Nationale de l'Informatique et des Libertés – CNIL) (protocol number 2019PI256-107). The CNIL is an independent administrative authority responsible for ensuring the protection of personal data contained in computer or paper files and processing. It ensures that data processing is at the service of the citizen and that it does not infringe on human identity, human rights, privacy, individual or public freedoms. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DRCI manages ethical issues and research quality; patients' data are checked and elaborated by Methodology, Data Management and Statistic Unit (Unité de Data Management et Statistique – UMDS), in accordance with Chapter IX of Law No. 78-17 of January 6, 1978 relating to data processing, files and freedoms. The DRCI, as study Promoter (which is not Investigator of the study), has signed a commitment to comply with the Methodology Reference (MR)-004 specification for data policy. This article was supported by a grant from the French Ministry of Health.

Protocol amendment

If a modification of the analysis plan provided for in this version of the protocol were to be made, this would be justified and validated by the DRCI.

Data management and confidentiality

The first author (IS) is the only person who has knowledge of the identity of the recruited patients and th3e results of patients' investigations. Data are collected in a protected computerized database only

accessible to first author. In accordance with the third paragraph of Article 56 of the Data Protection Act, the presentation of the results of the data processing may in no case allow the direct or indirect identification of the persons involved in the research.

Data collection will be carried out in accordance with the National Commission on Informatics and Liberties (Commission Nationale de l'Informatique et des Libertés) policy.

Patient's families give their oral consent to anonymous treatment of data to the first author (IS). Oral information as well as written details has been supplied to the family in order to provide the principles of the study (aims, data treatment modality). Family were also given the opportunity to refuse by written non consent to data use.

Protocol promotion and funding

This study has been selected as the award winner of "Neurosphynx 2021 call for project". NeuroSphinx rare diseases healthcare network coordinates the investigators concerned with rare pelvic and medullary malformations with sphincter damage. The diseases and malformations concerned are those which affect the marrow and the caudal pole. NeuroSphinx links together three Rare Disease Reference Centers, of which C - MAVEM is the specific one who organizes the caregiving of syringomyelia, Chiari and vertebral-medullary malformations. It promotes patients-health givers communication as well as research advances.

Thanks to this award, we have received financial support from Neurosphynx in order to contribute to the publication, and also to maintenance of the platform.

Sponsor

Direction for Research of the Nancy University Hospital as study Promoter. rue du Morvan, 54511 Vandoeuvre-lès-Nancy, France E-mail : **d.deoliveira@chru-nancy.fr**

NeuroSphinx rare diseases healthcare network call for project as award winner 2021 (IS).
NeuroSphinx - Hôpital Necker – Enfants Malades - 149 rue de Sèvres, 75015 Paris, France. Email: **contact@neurosphinx.fr**

Dissemination plan

The study's results will be submitted for publication in a peer-reviewed journal, conforming to the definition of the outcome presented in this protocol and will be discussed in dedicated specialized congress (European and International Society for Pediatric Neurosurgery, French Society for Pediatric Neurosurgery and European Society for Clinical Evaluation of Balance Disorders meetings). Results will be also presented in Neurosphynx's meetings, as award winner, thus allowing Chiari patients to be informed about.

The DRCI of the Nancy University Hospital is the owner of the data. Nevertheless, the main author and the principal investigator may dispose of these data and, in the respect of DRCI policy, for the purposes described above.

The observations done in this study could represent a starting point for other researches, maybe multicentric, and could give useful information about how to better manage Chiari's patients presenting with ENT symptoms.

Steering committee

It is composed by the main authors of this report, headed by Professor Philippe Perrin, principal investigator of the study.

Acknowledgments

The authors acknowledge Dr. Art Mallinson (Vancouver, British Columbia, CA) for his helpful advice in the final read-through of the manuscript.

Footnotes

- **Collaborators** Dr Art Mallinson, PhD.
- **Contributors** IS, OK and PP have conceived and designed the study; IS, OK, PP and AJ manage medical aspects of the patients; IS has written the paper while OK, PP and RT have participated in writing the paper; AP ensure the technical aspect of the posturography; RT cares about statistical analysis.
- **Funding** The project won a financial award from Neurosphynx rare diseases healthcare network, who nationally coordinates the Reference Center for Chiari malformation and Rare vertebro-medullary diseases.
- **Competing interests** The authors declare that there is not conflict of interest.

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FIGURES' LEGEND

Fig. 1 – Decision making flow chart for management of CM1 patients.

Fig. 2 – Posturographic results (Equitest®, NeuroCom, Clackamas, OR) in one of operated patients. Sensory Organization Test: the composite equilibrium score increased from 68 before surgery (Fig. 2 a) to 77 after surgery (Fig. 2b). Somatosensory (SOM), visual (VIS) and vestibular (VEST) ratios increased respectively from 90 to 96, 85 to 91 and 51 to 60 before to after the surgery.

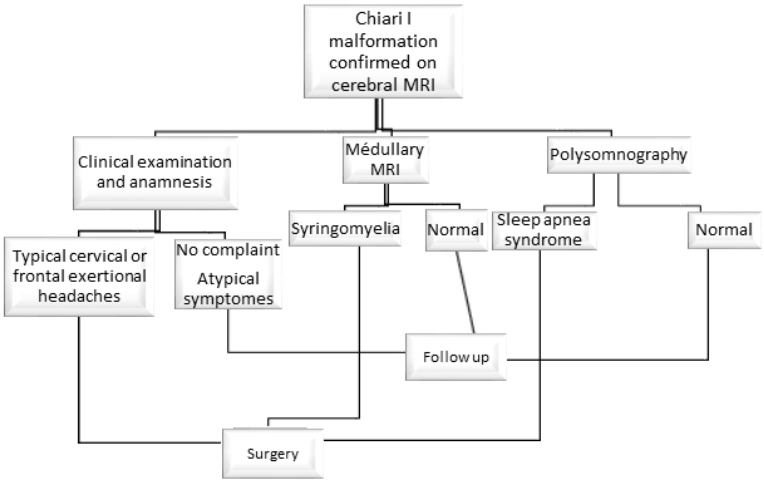

Fig. 1 – Decision making flow chart for management of CM1 patients.

532x361mm (38 x 38 DPI)

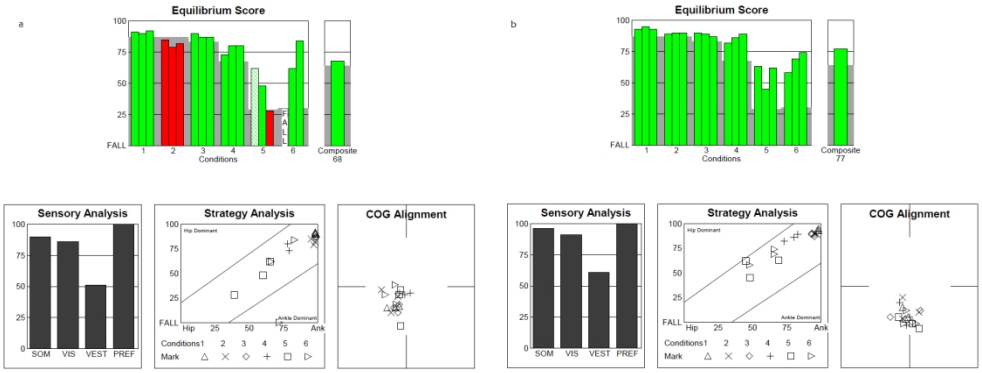

Fig. 2 – Posturographic results (Equitest®, NeuroCom, Clackamas, OR) in one of operated patient. Sensory Organization Test: the composite equilibrium score increased from 68 before surgery (Fig. 2 a) to 77 after surgery (Fig. 2b). Somatosensory (SOM), visual (VIS) and vestibular (VEST) ratios increased respectively from 90 to 96, 85 to 91 and 51 to 60 before to after the surgery.

1263x473mm (38 x 38 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Lines 1-3)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Lines 49, 342-43)**
	2b	All items from the World Health Organization Trial Registration Data Set **All items of the WHO Trial Registration Data are respected**
Protocol version	3	Date and version identifier **(Lines 45-46, 350)**
Funding	4	Sources and types of financial, material, and other support **(Lines 380-88, 421-23)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Lines 7-15, 417-20)**
	5b	Name and contact information for the trial sponsor **(Lines 390-94)**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(Lines 402-4)**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(Lines 410-11)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(Lines 60-105)**
	6b	Explanation for choice of comparators **(Lines 185-94)**
Objectives	7	Specific objectives or hypotheses **(Lines 125-33)**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(Lines 137-39)**

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **(Lines 166-71)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(Lines 144-64)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Lines 196-267)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(Lines 138-39)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **In this protocol, interventions are realised on the basis of medical arguments.**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(Lines 173-75)**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(Lines 269-311)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(Line 338)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(Lines 36,144)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(Line 166)**

Methods: Assignment of interventions (for controlled trials)
This protocol is not a randomized trial.

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Lines 325-31)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(Lines 178-81)**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Lines 325-25)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Lines 313-21)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **There are no additional analysis**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(Lines 333-34)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(Lines 335-36)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(Line 340)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **No auditing procedures have been planned**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Lines 347-62)**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(Lines 364-65)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Lines 375-78)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(NA)**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(Lines 368-378)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Line 424)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(Lines 368-72)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(NA)**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(Lines 396-407)**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(Lines 137-39)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(NA)**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **A model consent form has been provided**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(NA)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Postural control in Chiari I malformation: protocol for a paediatric prospective, observational cohort. Potential role of posturography for surgical indication.

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Postural control in Chiari I malformation: protocol for a paediatric prospective, observational cohort. Potential role of posturography for surgical indication.

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Keywords: Chiari I malformation; paediatric neurosurgery; posturography.

ABSTRACT

Introduction: Chiari I malformation (CM1) is an anatomical abnormality characterized by the cerebellar tonsils descending at least 5 mm below the foramen magnum. CM1 causes obstruction of cerebrospinal fluid (CSF) circulation as well as direct compression on the brainstem, thus causing typical consequences (syringomyelia), and typical clinical features (characteristic headaches and neurological impairment). Surgery is the only available treatment, indicated when symptomatology is present. However, sometimes patients have atypical complaints, which are often suggestive of otolaryngological (ENT) involvement. This may be difficult for a neurosurgeon to explain. Our study aims to investigate the relationship between one of these atypical symptoms, e.g. postural instability, in a paediatric population using a Computerized Dynamic Posturography (Equitest®, NeuroCom, Clackamas, OR). To our knowledge, there are no previously published studies carried out on children with Chiari I malformation, utilizing dynamic posturography.

Methods and analysis: forty-five children aged 6 to 18 years old presenting with radiologically confirmed CM1 and presenting ENT clinical complaints will be included in the study for a duration of 3 years. As primary endpoint, posturographic results will be described in the population study. Secondly, posturographic results will be compared between patients with and without indication for surgery. Finally, pre- and postoperative posturographic results, as well as CSF circulation quality at foramen magnum level, syringomyelia, sleep apnea syndrome, scoliosis and behavior will be compared in the operated patient group.

Ethics and dissemination: this protocol received ethical approval from the Clinical Research Delegation of Nancy University Hospital, in accordance with the National Commission on Informatics and Liberties (Commission Nationale de l'Informatique et des Libertés) (protocol number 2019PI256-107). Our data treatment was in accordance with the Methodology of reference MR-004 specification for data policy. The study findings will be disseminated via peer-reviewed publications and conference presentations, especially to the Neurosphynx's rare disease health care network.

Protocol registration number

CLINICALTRIALS n° NCT04679792 (17/12/2020).

Strengths and limitations of the study

- This is the first trial which evaluates postural control strategies in a paediatric population affected by Chiari I malformation using computerized dynamic posturography.
- Quantitative and qualitative data inherent to postural ability will be observed and collected, in order to ensure reproducibility of the research.
- This protocol could represent the starting point for a wider, multicenter study.
- This trial is a multidisciplinary approach to Chiari I malformation, combining neurosurgical, ENT and biomechanical expertise.
- The main limitation is that posturography can be unreliable in children under 6 years-old.

INTRODUCTION

Chiari I malformation (CM1) is a structural abnormality characterized by cerebellar tonsillar descent of at least 5 mm below the level of the foramen magnum (1), into the vertebral canal. Once considered to be rare, it is now quite often diagnosed incidentally due to the increasing utilization and sensitivity of neuroimaging, especially MRI. Although the true prevalence in the general population is difficult to establish, the imaging incidence in children younger than 18 years has been reported from 0.4 to 3.6% (2,3)

Initially reported in the XII century by Nicholas Tulp in its "Observationes Medicae" (4), its formal description has been attributed to Hans Chiari in 1896 (5,6). Despite CM1 is actually one of the most studied neurosurgical topics, some aspects concerning this malformation (i.e. pathogenesis, evolution and treatment) remain controversial (2), so that different studies are in progress with the aim of clarifying the natural history and best management of CM1 (7).

While 14% to 21% of people remain asymptomatic (8), most patients present with a constellation of clinical features which are diverse and which can impair their quality of life. The most typical symptom attributed to CM1 is pain; this paroxysmal symptom is usually localized to the occipital-cervical region and it is associated with a Valsalva maneuver such as coughing, laughing or sneezing. Other neurological symptoms or signs are related to brainstem or cranial nerve compression or distortion, and are represented by long tract sensitive-motor deficit, hyperreflexia, Babinski sign, sleep apnea syndrome and, less commonly, vocal cord paralysis, palatal weakness and dysarthria (9). If syringomyelia is associated, as in 45-75% of patients (10,11), one can also see a typical clinical expression such as distal-to-proximal weakness of the upper limbs with a cape-like suspended sensory loss. Less commonly, cerebellar syndrome with nystagmus, dysarthric speech and ataxia may be present (9).

Given the fact that the clinical presentation of CM1 is highly variable, and often accompanied by less than clear subjective somatic complaints (12), in everyday practice it is sometimes difficult to state whether CM1 is really symptomatic or not. Some neuro-otological manifestations (such as nystagmus, dizziness and imbalance) are reported in CM1, but these features have been described as "atypical" (13), thus creating confusion in interpretation.

Whether the malformation is symptomatic or not is of fundamental importance to determine if the patient is candidate for surgical intervention; surgery is the only possible treatment for this abnormality.

When analyzing CM1 from an anatomical point of view, however, it is not unreasonable to think that patients may present with symptoms and signs suggestive of otolaryngological (ENT) involvement (14). As a matter of fact, it is important to keep in mind that many of the pathways and structures responsible for balance and gait control (i.e. medial longitudinal fasciculus, spinocerebellar tracts, vestibulospinal fasciculus, reticulospinal fasciculus, vestibular nuclei and nerves) are located in the brainstem in the craniocervical region, feeding both afferent and efferent collateral fibers to the cerebellum.

Moreover, ataxia is rarely found on neurological standard clinical examination in CM1 patients and its formal characterization is difficult in the paediatric population.

For these reasons, we feel that detailed clinical evaluation, including objective testing might be advantageous in this population. Literature about instrumental imbalance evaluation in CM1 patients is scarce, although ataxia and dizziness are frequently described (9,15–18). We decided to evaluate one of these uncommon aspects in children, i.e. imbalance, using Computerized Dynamic Posturography (CDP) (Equitest®, Neurocom, Clackamas, OR) at our institution (LAPEM laboratory, Brabois University Hospital in Nancy, France). To our knowledge, this is the only study using CDP in children with CM1.

Preliminary search and pilot study selection

Initial research was conducted following four main axes:

- typical symptoms of CM1 reported in neurosurgical reviews,
- ENT involvement,
- developmental assessment of equilibrium control in children,
- dynamic posturography recordings in pediatric population.

Systematic review of the literature at the time of study design was performed using an Index Medicus and PubMed electronic database, looking for typical symptoms of CM1 reported in neurosurgical articles. ENT studies reporting the interest of neuro-otological evaluation in Chiari I patients were checked, and the following clinical features were individualized: nystagmus, dizziness, hearing loss and gait imbalance (19–34). Seven studies were selected to express the normal development of postural control in children (35–41), two of which underline the feasibility and effectiveness of Equitest® (39,42).

Posturographic evaluation in CM1 patients has been utilized in a study published in 2019 by Palamar et al. (43). Static posturography (Tetrax® Interactive Postural Balance System (Sunlight Medical Ltd, IT) was used in 36 adult subjects, trying to find a correlation between the risk of fall (Fall Index) and degree of tonsillar ectopia, as well as presence of syringomyelia. The authors did not report significant results, but found a more elevated Fall Index in patients with more than 1 cm tonsillar ptosis.

Study objectives

The aim of our research is to analyze the characteristics of balance control in a paediatric population presenting with CM1. This evaluation will be performed utilizing CDP (Equitest®). To our knowledge, no similar previous studies have been published.

We also wished to compare the CDP sensory organization test (SOT) patterns between patients with surgical cases of CM1 and non-surgical ones. Surgical indication, determined on the basis of actual neurosurgical criteria, will not be influenced by the results of this study.

Our study will also compare preoperative versus 3-months postoperative assessments with regard to (i) posturographic results, (ii) imaging results, (iii) symptomatology, (iv) sleep quality, (v) spinal balance (e.g. scoliosis) and (vi) behavior in the group of operated patients.

METHODS and ANALYSIS

Protocol design

This is a non-blinded, non-interventional, monocentric, multidisciplinary and prospective, observational, longitudinal clinical study. The ongoing results of the study will not influence surgical decisions.

Patients and Public Involvement

No patient was involved in the development of this study.

Population study

A total of 45 patients will be enrolled in the study for a duration of 3 years.

Inclusion criteria are:

- children aged from 6 to 18 years with radiologically confirmed CM1,
- children presenting clinical features suggesting ENT involvement (dizziness, nystagmus, gait impairment, motion sickness, malaises and atypical migraines which cannot be directly attributed to the CM1),
- children whose parents/guardians agreed to participation in the study, after being supplied detailed oral and written information.

Diagnosis of CM1 was made by the presence of a caudal displacement of cerebellar tonsils of at least 5 mm under the foramen magnum (more precisely, under McRae's line, a radiographic line drawn on a midsagittal section of MRI that connects the anterior and posterior margins of the foramen magnum). This is traditionally used as a reference to determine foramen magnum level (1) and is associated with problems of cerebrospinal fluid circulation at the foramen magnum level, and a possible brainstem compression.

Non-inclusion criteria are:

- Chiari malformation secondary to other complex pathology (e.g. craniostenosis, severe craniocervical malformation, intracranial hypertension, posterior fossa tumor);
- inability to stand on the CDP platform, due to cerebral palsy, severe behavioral troubles, severe visual impairment, or associated orthopedic pathologies;
- preexisting vestibular pathology;
- refusal of parent to allow use of the indexed personal data.

Study setting

Newly diagnosed CM1 patients recruited at Nancy University Regional Hospital (France) initially undergo neurosurgical evaluation to perform a complete clinical evaluation and precise anamnesis, that will be recorded in a survey, ensuring that no valuable information is missed.

Afterward, patients are systematically adressed to perform these two fundamental exams:

- medullary MRI, to check for syringomyelia,
- polysomnographic recording, to look for sleep apnea syndrome.

Patients who present clinical pictures such as dizziness, nystagmus, gait impairment, disabling motion sickness, malaise and atypical migraines which cannot be attributed to their CM1 will be referred for ENT assessment, including neuro-otological examination and CDP.

Group definition

Patients will be allocated into two groups:

- patients who will benefit from surgical intervention (followed up for several years after the intervention),
- patients in whom there is no indication for surgery (followed until adulthood to check for CM1 modification over time).

Choice of comparators

Partition of the patients into the two groups will be made following standard neurosurgical selection criteria for surgery. The decision for surgical intervention is supported by the following examinations: (i) anamnestic and clinical elements, (ii) cerebral and medullary MRI and (iii) polysomnography. A decision making flow chart is illustrated in Figure 1.

The criteria which lead the neurosurgeon to decide on surgical intervention are represented by the presence of at least one of the following aspects:

- characteristic symptomatology (most of all, exertional headaches, usually occipito-cervical, but also of frontal location; presence of symptoms of brainstem compression),
- syringomyelia,
- central sleep apnea.

Investigations

ENT assessment will be carried out in both surgical and non-surgical groups presenting with symptoms requiring specialist examination, as mentioned above. It will consist of a neuro-otological examination and clinical vestibular assessment, if deemed necessary.

The aims of the neuro-otological examination are to detect and differentiate cerebellar and vestibular signs, identify segmental or axial deviations, and rule out confounding associated factors.

A cerebellar syndrome is recognized by the finger to nose test (dysmetria), alternating hand movements (dysdiadochokinesis) and by the increase of the polygon in the Fukuda stepping test (cerebellar ataxia).

With regards to a vestibular syndrome, the consequences of a vestibular lesion can be appreciated by evaluating the vestibulo-ocular pathway (evidenced by the presence of nystagmus), the vestibulo-spinal pathway (which can produce instability), the vegetative pathway (linked to nausea and vomiting) and the perceptual (vestibulo-cortical) pathway (which can produce true vertigo). Videonystagmography, along with normal caloric vestibular assessment, is very helpful at suggesting brainstem pathology and ruling out peripheral vestibular involvement (21).

Patients are also evaluated for the presence of nystagmus, which is usually due to peripheral or central vestibular impairment.

Other evaluated factors included vergence insufficiency, refraction disorders, or other visual correction. It is sometimes necessary to ask for a complementary ophthalmological or orthoptic assessment.

Vertigo or dizziness can have multiple causes in the same patient and will be accurately assessed. The diagnosis of the type of vertigo relies mainly upon the history taken from the patient and the clinical examination. Any history of head trauma and falls, headache, drug intake, and motion sickness susceptibility is noted. If spells of true vertigo are occurring, they need to be precisely described (starting date, number, frequency, duration, intensity) in order to determine an eventual evolutionary pattern. The following triggers are sought: head versus trunk movement, movement of the head in space, quick standing, stressing situations (cardio-vascular origin). So called “false vertigo” should be eliminated (44). Vertigo or unsteadiness can be associated with sensorineural and conductive hearing loss. Otitis media and previous ear surgery are noted. Complaints of tinnitus should also be addressed.

Otoscopic examination will also be carried out, with tympanometry and acoustic reflex test recordings (Interacoustics, Middelfart, Denmark) and determining hearing thresholds (pure-tone air and bone-conduction thresholds) in tone audiometry (from 250 Hz to 8000 Hz) and intelligibility in speech tests (Interacoustics).

After that, CDP will be carried out to determine balance control performances.

CDP (Equitest®, NeuroCom, Clackamas, OR) assesses global balance performance and relative weight of sensory information (visual, vestibular, and somatosensory) involved in balance control. The Equitest balance system consists of a dual platform with two footplates connected by a pin join. The footoplates are supported by five force transducers. The computer calculates the center of foot

pressure (CoP) and the vertical component of the center of gravity (CoG), using the subject's height entered by the operator. When a subject stands with ankles centered over the stripe on the dual platform, with feet an equal distance laterally from the center line, he is in the a position called "electrical zero position", which serves as a reference point for the calculation of sway angles.

The sensory organization test (SOT) consists of three 20-sec trials under six different sensory conditions in which the surface and/or visual surround (i.e. sensory inputs) are systematically manipulated (so-called "sway referencing"). (Table 1) (43–46).

Postural control test		
Name	Situation	Sensory consequences
Condition 1	Fixed support, eyes open	-
Condition 2	Fixed support, eyes closed	Vision absent
Condition 3	Fixed support, SR surround	Altered vision
Condition 4	SR support, eyes open	Altered proprioception
Condition 5	SR support, eyes closed	Vision absent, altered proprioception
Condition 6	SR support SR surround	Altered vision and proprioception

Table 1: Computerized dynamic posturography. Sensory organization test (Equitest®, NeuroCom, Clackamas, OR). Determination of the six conditions. SR, sway-referenced (42,46,47).

Examination in eyes closed situations (conditions 2 and 5) may be made more complex by 30° rhythmic flexo-extension movements of the head, to better evaluate the somatosensory component of vestibular function and cervical muscles (see below). This might be of particular interest in patients with Chiari malformation. To protect against falls, patients wear a safety harness connected to the ceiling and an operator stands within reaching distance. An equilibrium score (ES) is calculated by comparing the subject's anterior-posterior sway during each 20 s SOT trial to the maximal theoretical sway limits of stability, which is based on the individual's height and size of the base of support. It represents an angle (8.0 anteriorly and 4.5 posteriorly) at which the subject can lean in any direction before the center of gravity would move beyond a point that allows him/her to remain upright (i.e., point of falling). The following formula is used to calculate the ES:

$$\text{Equilibrium} = 12.5° - (\theta\text{max} - \theta\text{min}) / 12.5° \times 100$$

where θmax indicates the greatest antero-posterior CoG sway angle, θmin indicates the lowest antero-posterior CoG sway angle. Lower sways lead to a higher ES, indicating a better balance control performance (a score of 100 represents no sway, while 0 indicates sway that exceeds the limit of stability, resulting in a fall). Table 2 shows CES and sensory ratios calculation's method.

Name	Equation	Significance
Composite score	[C1 + C2 + 3 (C3 + C4 + C5 + C6)] / 14	Evaluate global balance performance. A low score represents poor postural control
Somatosensory ratio	C2 / C1	Ability to use somatosensory input to maintain balance (even when visual cues are removed). A low score suggests poor use of somatosensory references
Visual ratio	C4 / C1	Ability to use visual input to maintain balance (even when somatosensory cues are altered). A low score suggests poor use of visual references
Vestibular ratio	C5 / C1	Ability to use vestibular input system to maintain balance (even when visual cues are removed and somatosensory cues are altered). a low score suggests poor use of vestibular cues or that vestibular information is unavailable
Visual preference ratio	C3 + C6 / C2 + C5	Degree to which patient relies on visual information to maintain balance (correct/incorrect information). A low score suggests reliance on visual cues even when they are inaccurate

Table 2: Computerized dynamic posturography. Sensory organization test (Equitest®, NeuroCom, Clackamas, OR). Significance of composite score and sensory ratios.

Posturography is also useful in evaluation of the patient with multiple pathologies affecting several components of the sensorimotor chain (inner ear, vision, and somesthetic). (48).

An example of CDP preoperative and postoperative results is illustrated in the Figure 2.

Association between Chiari malformation and scoliosis is well known; scoliosis can be a factor in balance impairment (49) and altered oculomotor functions (50). Accordingly, these factors will also be taken into account in the assessment.

Outcomes

Primary outcome

The Composite Equilibrium Score (CES) will be our primary endpoint, along with the reported visual, somesthetic and vestibular components.

We also will carry out the following evaluations:

- A Head Shake Sensory Organization Test (details of this assessment are outlined in the literature (51–54) consisting during 20 sec of repetitive forward and backward flexions of the head, these head tilts provocative condition of 30° in the pitch plane (cervical flexion / extension) at 0.33 Hz stimulating the cervical proprioception and muscles, as well as the two inner ears. This sensory stimulation was tested in eyes closed condition, both stable (during condition 2) and sway-referenced platform (during condition 5). We feel it important to assess these parameters as these patients may present with cervical pain and muscle impairment.

- Lateral displacements of the center of gravity, used to quantify the postural sway in the medial-laterally plane.

We also wish to evaluate postural strategies that will be adopted. As outlined in the literature, there are two strategies; a bottom-up regulation model, where the body is oscillating like an inverted pendulum ("ankle strategy"), and a top down strategy (a pattern favoring visual preference involved ("hip strategy"). According to this model, postural control in the sagittal plane is by default exerted around the ankle joint and then (if the postural challenge increases) by the hip joint (55–57)

Secondary outcome

The secondary outcomes are the following.

- CDP results comparison between surgical and not surgical patients,
- Efficacy of surgical intervention to restore cerebrospinal fluid circulation at foramen magnum level.

A single observer (IS) will be in charge of assessing the radiological assessments by comparing pre-operative and 3 months' postoperative MRI, using a three-point scale: 0 = any modification appreciated; 1 = improved tonsillar ptosis; 2 = resolved tonsillar ptosis with reappearance of a cisterna magna.

- Effectiveness of surgical intervention on a preexisting syringomyelia.

Improvement will be considered when the cavity's size (maximum anteroposterior diameter) is reduced by at least 30% between pre-operative and 3 month's postoperative medullary MRI. Stability will be considered in case of cavity's size reduction from 0% to less than 30%, while any degree of increase in size will be considered as aggravation.

- Efficacy of surgical intervention to improve sleep quality.

In case of preexisting apnea syndrome before surgery, evolution in the ratio between total and partial respiratory interruption (i.e. apnea/hypopnea index) between pre-operative and 3 month's postoperative polysomnography will be considered. A reduction of at least 50% in this ratio will be considered as improvement.

- Effectiveness of surgical intervention to arrest vertebral imbalance (scoliosis).

In case of preexisting vertebral imbalance, corresponding to a Cobb's angle over 10°, none or minimal Cobb's angle change (< 5°) of the preexisting scoliosis will be considered as a favorable outcome.

- Influence of surgery on patient's behavior (Yes/No).

Based on parents' feelings at least 3 months after surgical intervention, change in patient's behavior (Yes/No) will be assessed at a routine follow up.

Statistical methods

Primary outcome

Data will be analyzed with counts and percentages for qualitative variables and means standard deviation or median and extreme values for quantitative variables (depending on the nature of the distribution).

Secondary outcomes

Intergroup comparison of posturographic results will be performed using Student's t-test or Mann–Whitney U test depending on the nature of the distribution. Comparison between "Before surgery" and "After surgery results" will be performed using Mc Nemar test or symmetry test categorical variables and Student's test or Wilcoxon's test on paired series for continuous variables.

Data collection method

The data are collected by the principal investigator in an electronic and anonymous database which is password protected and stored on the principal investigator's professional computer.

Data collection will be carried out in accordance with the National Commission on Informatics and Liberties (Commission Nationale de l'Informatique et des Libertés) policy.
During the study, the collection of data will be interrupted and the data previously collected will not be used if the person participating in the research objects to the use of their data.

Data monitoring: formal committee and interim analysis

No data monitoring committee has been appointed, due to the absence of recruitment problem and inclusion criteria based on neurosurgical arguments.

An interim analysis of outcomes has not been planned, due to the prompt interpretation of investigation's results.

Timeline

Patients' data are collecting from September 2020 to March 2023

Adverse effects

No adverse effect of the proposed investigation is conceivable.

Pre-registration

This protocol has been registered in ClinicalTrial.gov, identifier CLINICALTRIALS NCT04679792 (17/12/2020). Log in required to access records.

ETHICS AND DISSEMINATION

Approvals

This protocol received ethical approval from the Delegation for Clinical Research and Innovation (Délégation à la Recherche Clinique et à l'Innovation – DRCI) of the Nancy University Hospital, in accordance with the National Commission for Computing and Liberties (Commission Nationale de l'Informatique et des Libertés – CNIL) (protocol number 2019PI256-107). The CNIL is an independent administrative authority responsible for ensuring the protection of personal data contained in computer or paper files and processing. It ensures that data processing is at the service of the citizen and that it does not infringe on human identity, human rights, privacy, individual or public freedoms. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DRCI manages ethical issues and research quality; patients' data are checked and elaborated by Methodology, Data Management and Statistic Unit (Unité de Data Management et Statistique – UMDS), in accordance with Chapter IX of Law No. 78-17 of January 6, 1978 relating to data processing, files and freedoms. The DRCI, as study Promoter (which is not Investigator of the study), has signed a commitment to comply with the Methodology Reference (MR)-004 specification for data policy. This article was supported by a grant from the French Ministry of Health.

Protocol amendment

If a modification of the analysis plan provided for in this version of the protocol were to be made, this would be justified and validated by the DRCI.

Data management and confidentiality

The first author (IS) is the only person who has knowledge of the identity of the recruited patients and th3e results of patients' investigations. Data are collected in a protected computerized database only accessible to first author. In accordance with the third paragraph of Article 56 of the Data Protection Act, the presentation of the data processing results may in no case allow the direct or indirect identification of the persons involved in the research.

Data collection will be carried out in accordance with the National Commission on Informatics and Liberties (Commission Nationale de l'Informatique et des Libertés) policy.

Patient's families give their oral consent to anonymous treatment of data to the first author (IS). Oral information as well as written details has been supplied to the family in order to provide the principles of the study (aims, data treatment modality). Family were also given the opportunity to refuse by written non consent to data use.

Protocol promotion and funding

This study has been selected as the award winner of "Neurosphynx 2021 call for project". NeuroSphinx rare diseases healthcare network coordinates the investigators concerned with rare pelvic and medullary malformations with sphincter damage. The diseases and malformations concerned are those which affect the marrow and the caudal pole. NeuroSphinx links together three Rare Disease Reference Centers, of which C - MAVEM is the specific one who organizes the caregiving of syringomyelia, Chiari and vertebral-medullary malformations. It promotes patients-health givers communication and research advances.

Thanks to this award, we have received financial support from Neurosphynx in order to contribute to the publication, and also to maintenance of the posturography.

Sponsor

Direction for Research of the Nancy University Hospital as study Promoter. Vandoeuvre-lès-Nancy, France. E-mail : **d.deoliveira@chru-nancy.fr**

NeuroSphinx rare diseases healthcare network call for project as award winner 2021 (IS).
NeuroSphinx - Hôpital Necker, Paris, France. Email: **contact@neurosphinx.fr**

Dissemination plan

The study's results will be submitted for publication in a peer-reviewed journal, conforming to the definition of the outcome presented in this protocol and will be discussed in specialized congress (European and International Society for Paediatric Neurosurgery, French Society for Pediatric Neurosurgery and European Society for Clinical Evaluation of Balance Disorders meetings). Results will be also presented in Neurosphynx's meetings, as award winner, thus allowing Chiari patients to be informed about.

The DRCI of the Nancy University Hospital is the owner of the data. Nevertheless, the main author and the principal investigator may dispose of data and, in the respect of DRCI policy, for the purposes described above.

The observations done in this study could represent a starting point for other researches, maybe multicentric, and could give useful information about how to better manage Chiari's patients presenting with ENT symptoms.

Steering committee

It is composed by the main authors of this report, headed by Professor Philippe Perrin, principal investigator of the study.

Acknowledgments

The authors acknowledge Dr. Art Mallinson (Vancouver, British Columbia, CA) for his helpful advice in the final read-through of the manuscript.

Footnotes

- **Collaborators** Dr Art Mallinson, PhD.
- **Contributors** IS, OK and PP have conceived and designed the study; IS, OK, PP and AJ manage medical aspects of the patients; IS has written the manuscript while OK, PP and RT have participated in writing it; AP realizes the posturographic recordings; TR cares about statistical analysis.
- **Funding** The project won a financial award from Neurosphynx rare diseases healthcare network, who nationally coordinates the Reference Center for Chiari malformation and Rare vertebro-medullary diseases.
- **Competing interests** Authors declare that there is not conflict of interest.

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FIGURES' LEGEND

Fig. 1 – Decision making flow chart for management of CM1 patients.

Fig. 2 – Posturographic results (Equitest®, NeuroCom, Clackamas, OR) in one of operated patients. Sensory Organization Test: the composite equilibrium score increased from 68 before surgery (Fig. 2 a) to 77 after surgery (Fig. 2b). Somatosensory (SOM), visual (VIS) and vestibular (VEST) ratios increased respectively from 90 to 96, 85 to 91 and 51 to 60 before to after the surgery.

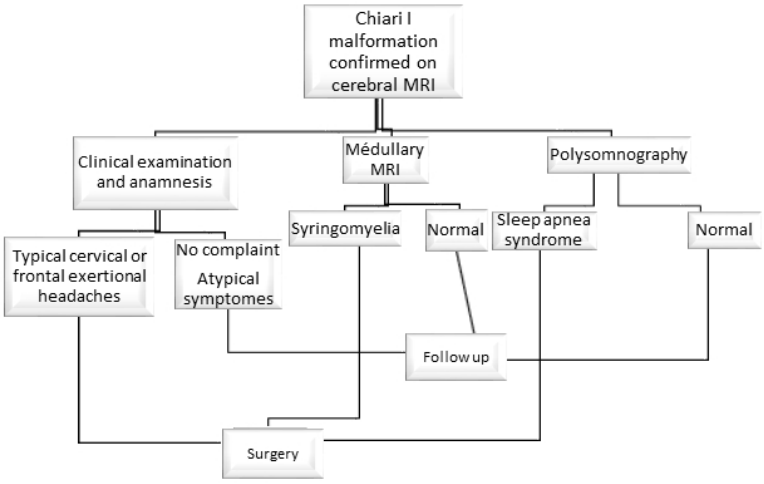

Fig. 1 – Decision making flow chart for management of CM1 patients.

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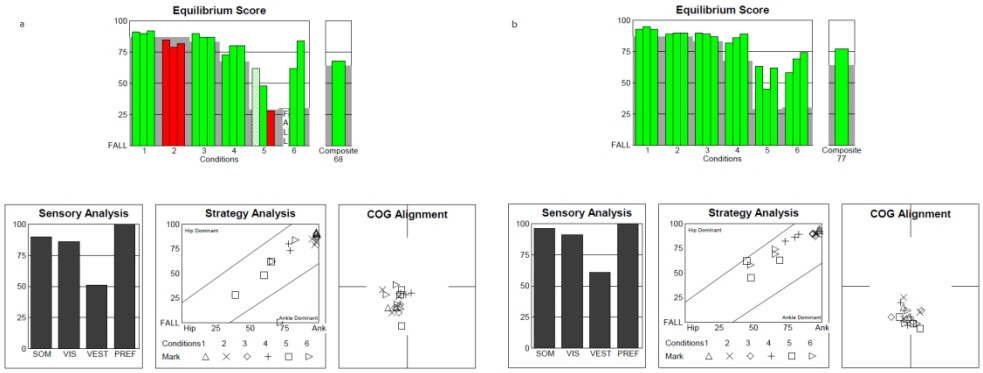

Fig. 2 – Posturographic results (Equitest®, NeuroCom, Clackamas, OR) in one of operated patient. Sensory Organization Test: the composite equilibrium score increased from 68 before surgery (Fig. 2 a) to 77 after surgery (Fig. 2b). Somatosensory (SOM), visual (VIS) and vestibular (VEST) ratios increased respectively from 90 to 96, 85 to 91 and 51 to 60 before to after the surgery.

1263x473mm (38 x 38 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(Page 1 Lines 1-3)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(Page 1 Lines 49-50; Page 9 LIne 345-346)**
	2b	All items from the World Health Organization Trial Registration Data Set **All items of the WHO Trial Registration Data are respected**
Protocol version	3	Date and version identifier **(Page 1 Line 45; Page 9 Line 353)**
Funding	4	Sources and types of financial, material, and other support **(Page 10 Lines 390-391; Page 11 Lines 424-426)**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(Page 1 Lines 5-15, Page 11 Lines 424-426)**
	5b	Name and contact information for the trial sponsor **(Page 10 Lines 393-396)**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(Page 10 Lines 405-407)**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(Page 10 Lines 413-414)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(Pages 2-3 Lines 62-107)**
	6b	Explanation for choice of comparators **(Page 5 Lines 186-195)**

Objectives	7	Specific objectives or hypotheses **(Page 3 Lines 127-135)**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non inferiority, exploratory) **(Page 3 Lines 139-141)**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **(Page 4 Lines 167-176)**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(Page 4 Lines 145-165)**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(Page 5-6 Lines 197-270)**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(Page 3 Lines 140-141)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **In this protocol, interventions are realised on the basis of medical arguments.**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **There are not concomitant care and intervention that are permitted or prohibited during our trial.**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(Pages 7-8 Lines 272-314)**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(Page 9 Line 341)**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(Page 1 Line 36; Page 3 Line 145)**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **There are not supplementary strategy for achieving adequate enrolment.**

Methods: Assignment of interventions (for controlled trials)
This protocol is not a randomized trial.

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(Page 8 Lines 328-333)**

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **This is not an intervention protocol and follow up is programmed (and respected by the patients) for medical reasons.**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(Page 9 Lines 328-329)**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(Page 8 Lines 317-324)**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **There are no additional analysis.**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Not applicable (NA).**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(Page 9 Lines 336-339)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(Page 9 Lines 338-339)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(Page 9 Line 343)**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **No auditing procedures have been planned.**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(Page 9 Lines 350-365)**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(Page 9 Lines 367-368)**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(Page 10 Lines 378-381)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(NA)**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(Page 10 Lines 371-377)**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(Page 11 Line 427)**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(Page 10 Lines 371-75)**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(NA)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(Page 10 Lines 399-410)**
	31b	Authorship eligibility guidelines and any intended use of professional writers These aspects have been intended in the respect of DRCI policy **(Page 11 Lines 420-423)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **(NA)**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **A model consent form has been provided**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(NA)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT