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REVIEW ARTICLE

The management of Chiari malformation type 1 and syringomyelia in children: a review of the literature

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Abstract

In anticipation of the "Chiari and Syringomyelia Consensus Conference" held in Milan in 2019, we performed a systematic literature review on the management of Chiari malformation type 1 (CM1) and syringomyelia (Syr) in children.

We aimed to summarize the available evidence and identify areas where consensus has not been reached and further research is needed.

In accordance with PRISMA guidelines, we formulated seven questions in Patients-Interventions-Comparators-Outcomes (PICO) format. Six PICOs concerned CM1 children with/without additional structural anomalies (Syr, craniosynostosis, hydrocephalus, tethered cord, and cranio-vertebral junction anomalies), and one PICO Syr without CM1. We searched Medline, Embase, Cochrane, and NICE databases from January 1, 1999, to May 29, 2019. Cohort studies, controlled and randomized clinical trials (CCTs, RCTs), and systematic reviews were included, all pertinent only to patients ≤ 18 years of age. For CM1, 3787 records were found, 460 full texts were assessed and 49 studies (46 cohort studies, one RCT, and two systematic reviews) were finally included. For Syr, 376 records were found, 59 full texts were assessed, and five studies (one RCT and four cohort studies) were included. Data on each PICO were synthetized narratively due to heterogeneity in the inclusion criteria, outcome measures, and length of follow-up of the included studies.

Despite decades of experience on CM1 and Syr management in children, the available evidence remains limited. Specifically, there is an urgent need for collaborative initiatives focusing on the adoption of shared inclusion criteria and outcome measures, as well as rigorous prospective designs, particularly RCTs.

Keywords Chiari malformation type 1 · Syringomyelia · Literature review · Children · Management · Outcome

Introduction

Chiari malformation type 1 (CM1) and syringomyelia (Syr) are increasingly diagnosed due to both the widespread use of magnetic resonance imaging (MRI) and increased clinical

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awareness [1, 2]; however, despite the accumulation of experience, the management of these disorders still poses clinical challenges.

CM1, radiologically defined by the position of the cerebellar tonsils herniated through the foramen magnum of five mm or more, constitutes a heterogeneous group of clinical and radiological conditions. It can be diagnosed as an isolated anomaly or in association with skeletal abnormalities of the cervical spine and cranio-vertebral junction (CVJ), Syr, craniosynostosis, hydrocephalus, tethered cord, and in a wide range of syndromic or non-syndromic clinical conditions [3, 4]. Children may present as asymptomatic or with subtle and not strictly specific signs and symptoms as well as with signs and symptoms related to associated pathologies [1, 4]. As a result, CM1 symptomatic children represent an issue for clinicians who, after making every effort to exclude all other non-Chiari origins of patient's symptoms, judge symptoms as Chiari-related primarily based on experience and personal judgment [1].

Currently, the only treatment to reduce symptoms is posterior fossa decompression surgery with or without duraplasty, with or without excision of the cerebellar tonsils. However, there is no complete consensus on whether, when, and how to treat children with CM1; uncertainty arises from the variability of presentation of CM1 and the paucity of data on the natural history of untreated patients and the long-term outcome of those treated.

Syr refers to a longitudinally oriented fluid-filled cavity of any size in the spinal cord expanding from the region of its largest diameter in the upper and/or lower direction. The definition, diagnosis, and classification of Syr still raise many questions as not every fluid-filled cavitation of the spinal cord deserves the diagnosis of Syr, and the distinction between Syr and central canal dilatation or hydromyelia may be difficult [5–7].

It is universally accepted that Syr is not a disease of the spinal cord on its own, but a secondary event related to a disturbance of the cerebro-spinal fluid (CSF) flow for spinal cord tethering, intramedullary tumors, cysts, arachnoiditis due to previous infections, and traumatic events. Therefore, when Syr is present, further diagnostic efforts must be undertaken to determine the underlying pathology and consequently to focus the treatment because the natural history of significant Syr is a progressive loss of neurological function over years or decades [7].

As experience accumulates, indications for management are evolving but, despite the growing body of literature on CM1 and Syr, a lot of issues remain unclear.

In this scenario, CM patients' associations are growing, identifying referral centers and promoting international conferences to bring experts together and share a common course of action.

In anticipation of the organization of the "Chiari and Syringomyelia Consensus Conference" held in Milan in 2019 [8, 9], as members of the scientific panel we performed a systematic literature review regarding the management of CM1 with or without other structural anomalies and Syr without CM1 in children.

We aimed to summarize the available evidence and to identify areas where the consensus has yet to be reached and further research is needed.

Methods

We performed a systematic search of the literature on the management of CM1 with or without associated structural anomalies (Syr, craniosynostosis, hydrocephalus, tethered cord, and CVJ anomalies), and Syr without CM1 in children, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [10].

Formulation of the clinical questions

Seven clinical questions were formulated in Patients-Interventions-Comparators-Outcomes (PICO) format by a panel of one pediatric neurologist (VS), three neurosurgeons (LM, PP, LV), one neurophysiologist (PC). Six PICOs concerned CM1 with or without associated malformations, and one Syr without CM1 (Appendix 1 Table 9).

Data sources and search strategy

An expert librarian (SM) drew the searches for the following databases: Medline-PubMed, Embase, The Cochrane Library, and NICE (National Institute for Health and Care Excellence, UK). Combinations of the following subject headings and keywords were used across all databases: "Arnold Chiari malformation" or "CM1" or "CIM" and several synonyms. A specific search strategy was drawn for PICO 7. The full electronic search strategies are included in Appendix 2.

The searches were launched on May 29, 2019, to prepare the "Chiari and Syringomyelia Consensus Conference" to be held in Milan in November 2019 [8, 9].

Eligibility criteria

Participants were children (18 years or younger), with a diagnosis of CM1 with or without associated malformations, and Syr without CM1. Children with CM non-type 1, myelomeningocele, and spina bifida were excluded. Studies with mixed population (for age range or diagnosis) were considered only if data for children were available. No restrictions were made in terms of interventions and

comparators. The outcome measures we considered were the following: change or appearance of symptoms and signs, change in the degree of herniation of the cerebellar tonsils, change or appearance of syringomyelia and hydrocephalus, CSF flow changes, surgical complications, need for operation or reoperation.

Eligible studies were prospective and retrospective cohort studies, controlled clinical trials (CCTs), randomized controlled clinical trials (RCTs), and systematic reviews/meta-analyses published from January 1, 1999, to May 29, 2019. We excluded case reports (up to 3 children), abstracts in congress proceedings, and studies published in languages other than English.

Identification of relevant studies

Study selection was performed by a trained researcher (MF). After deleting duplicate citations, the title and abstract of all publications were screened to assess suitability for inclusion. Publications considered potentially eligible were read in full by two researchers (MF, LV), and a third researcher (AS) was involved when consensus on the study was not achieved.

Data synthesis

For each included study, information was extracted by one researcher (MF) and checked by another (AS). These researchers appraised the quality of the studies using section A of the Critical Appraisal Skills Programme (CASP) tool for cohort studies [11] and following Higgins et al. for CCTs and RCTs [12]. Results were synthesized qualitatively.

Results

The search strategy retrieved 3787 articles for PICOs 1–6. After duplication removal, 2200 potentially relevant publications were identified. Following the selection process depicted in Fig. 1, 460 full texts were read and evaluated and 49 articles were considered eligible for this review, including two systematic reviews, one RCT, and 46 case series (Fig. 1).

For PICO 7, 376 records were screened, 59 articles were assessed, and five studies, including one RCT and four case series, were encompassed in the review (Fig. 2).

Results are presented by PICO, and followed by a short commentary.

PICO 1: For asymptomatic CM1 children, which are the effects of neurosurgery versus conservative management on the clinical and radiological outcome?

PICO 2: For symptomatic CM1 children, which are the effects of neurosurgery versus conservative management on the clinical and radiological outcome?

To answer PICO 1 and 2 (Table 1 and Table 2), we identified only one cohort study that compared the effects of surgical treatment versus conservative management in 95 CM1 children, both asymptomatic and symptomatic, monitored with long-term clinical and radiological follow-up [13]. Additional eight cohort studies focused on the short- and long-term outcomes of asymptomatic and mildly symptomatic CM1 children managed without surgery [14–21], and four cohort studies described the short- and long-term effects of surgery in symptomatic CM1 children [1, 3, 22, 23].

All retrospective except for two [20, 22] collectively these studies reported the data of:

- 930 CM1 children treated conservatively. Of these, 230 (24.7%) were classified as asymptomatic at inception, 105 (11.3%) as mildly symptomatic, while for 595 (64%) no clear distinction was made between asymptomatic and mildly symptomatic [13–21];
- 558 CM1 children treated with surgery for their clinical and/or neuroradiological picture [1, 3, 13, 22, 23]. We omitted the series of 130 children described by Tubbs et al. in 2003 since these data were part of a subsequent study [1, 3].

In the group of patients managed conservatively, when the information was available, mildly symptomatic children ranged from 11.3% [16] to 68.6% [13]. During follow-up, ranging from 9 months to 19 years, the clinical outcome was characterized by stability or improvement in most children (from 72.7 to 100%). Resolution of symptoms was reported in a minority of cases; worsening of symptoms was reported from 4.8 to 28.6%, and new symptoms occurred in 6.3% of children. As for the radiological outcome, tonsillar ectopia remained stable in 64.1% of children, improved in 25.7%, worsened in 6.3%, and resolved in 5.9%. Similarly, Syr unfrequently worsened (up to 15.4%) or appeared (up to 21.4%). During follow-up, 50 of the 930 patients (5.3%) required surgical treatment, 32 (64%) for clinical reasons and 18 (36%) for radiological causes represented by Syr in 14 and ventriculomegaly in four [13–21].

Operated CM1 children were followed up from 2 months to 18 years, showing clinical improvement from about 80% up to 100%, and stabilization or improvement of Syr in near all subjects [1, 3, 13, 22, 23]. Indeed, in the group of 500 operated children with posterior fossa decompression and duraplasty, only 1.4% of 285 Syr increased [3]. Moreover, new or increased Syr appeared in four of 25 (16%) operated CM1 children in the study by Pomeraniec et al. [13]. None of the authors reported worsening of tonsillar herniation or

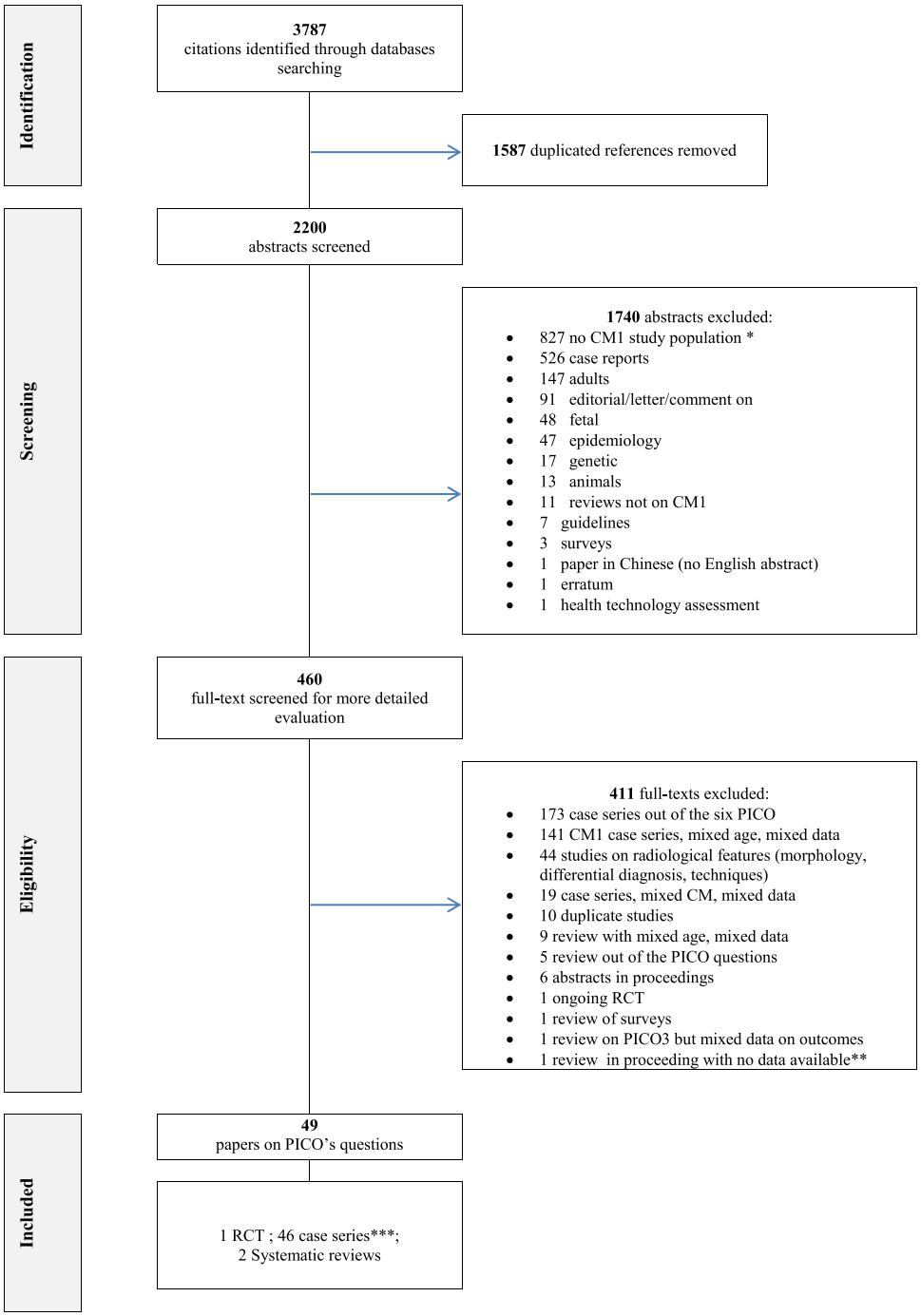

Fig. 1 Flowchart of the selection process (PICO1-6). *Any condition/symptom in which the focus of the study was that symptom/condition and CM1 was accidentally discovered (i.e., idiopathic scoliosis, headache, vertigo, etc.); **authors were contacted, but no replay was received; ***some papers cover more than one PICO: 9 for PICO1; 8 for PICO2; 21 for PICO3; 8 for PICO4; 4 for PICO5; 2 for PICO6

cerebellar prolapse, but an improvement was described in the 25 children operated by Pomeraniec et al. with an average ascent of 10 mm, and in seven out of 22 (31.8%) children operated by Knerlich-Lukoschus et al. with an ascent of more than two mm upwards [13, 23]. The complication rate was very low (from 0 to 2.4%) and a new operation was required in 3% [3] to 20% of children [13]; in most instances, reoperation was for persistent Syr, rarely for unchanged symptoms.

Commentary

In the interval period we considered for the literature review, 13 pediatric case series were published with the aim of (a) describing the natural history of asymptomatic or minimally symptomatic CM1 children, (b) determining the frequency with which such patients eventually develop symptoms requiring surgical treatment, (c) identifying clinical and radiological predictors or risk factors and appropriate

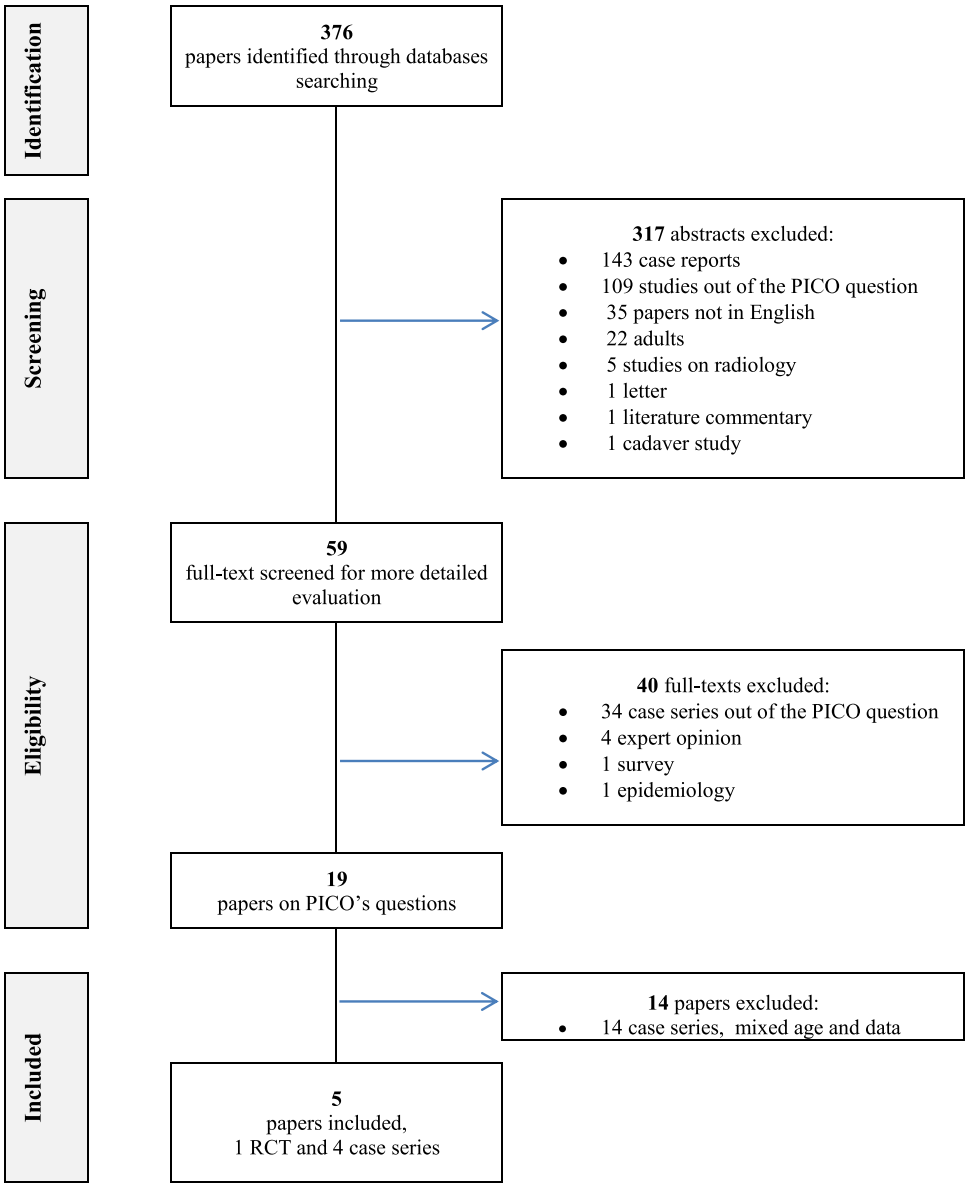

Fig. 2 Flowchart of the selection process for PICO 7

surgical candidates in this population, (d) analyzing surgical effects. Such information is of great importance for the evidence-based management and surgical decision-making in CM1 children.

The studies about conservative management, all retrospective except for one [20], were not conducted with overlapping inclusion criteria: some included only asymptomatic patients [18, 20], others even those mildly symptomatic [13–17, 19, 21]; some only patients without Syr [20, 21] and/or ventriculomegaly [16, 20, 21], others also patients who presented with such radiological findings [13–20]. Furthermore, the follow-up was not homogeneous either in terms of timing or method; indeed, in some studies, the patients were evaluated only by neurosurgeons [14], while in others also by pediatric neurologists and/or otolaryngologists [17, 21], and in some cases with the aid of neurophysiological investigations such as evoked potentials and polysomnography [13, 18]. Some patient groups were evaluated both clinically and radiologically, while other patients had no follow-up imaging studies [16, 19]. Finally, the surgical criteria were clearly specified in only two articles [19, 21] because not all centers followed a rigorous protocol to determine whether to surgically treat a CM1 child [17].

However, despite these differences and biases, the researchers came to similar conclusions: CM1 children who initially do not require surgery as they are asymptomatic or mildly symptomatic generally follow a benign course and can be managed conservatively as only about 5% of them during follow-up require surgical treatment for clinical or radiological reasons (Syr or ventriculomegaly).

The few published studies on the effects of surgical treatment [1, 3, 22, 23] are all retrospective, with the exception of

Table 1 Characteristics of the included studies for PICO 1

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Novegno et al. (2008)*	11 asymptomatic CM1 (50% of 22 CM1 children) - 1 with syrinx - 4 with ventriculomegaly	5.1 years (1–14)	Retrospective cohort, single center	Conservative	NA	01/1988-11/2007	6.6 years (3–19)	Clinical MRI Surgery
Aitken et al. (2009)	19 asymptomatic CM1 (37% of 51 CM1 diagnosis) - 2 with syrinx	11 years§ (NR)	Retrospective cohort, multicenter	Conservative	NA	01/1997-12/1998	6.4 years§ (NR)	Clinical MRI Surgery
Benglis et al. (2011)	110 asymptomatic CM1 (88.7% of 124 CM1 children) - 5 with syrinx	7.0 years§ (1–20)	Retrospective cohort, single center	Conservative	NA	07/1999–07/2008	2.8 years§ (1–8.6)	Clinical MRI Surgery
Massimi et al. (2011)*	16 asymptomatic CM1 - 2 with syrinx - 4 with ventriculomegaly	6.7 years (1–16)	Retrospective cohort, single center	Conservative	NA	01/1990–11/2008	5.8 years (3–12)	Clinical MRI Surgery
Strahle et al. (2011)	147 asymptomatic and mildly symptomatic CM1 ≥ 1 year clinical and MRI follow-up ($n=242$ excluded) - 13 with syrinx	7.7 years§ (NR)	Retrospective cohort, single center	Conservative	NA	11/1997–08/2008	Clinically 4.6 years§ (NR) By MRI 3.8 years§ (NR)	Clinical MRI Surgery
Killeen et al. (2015)	21 asymptomatic or mildly symptomatic CM1 ≥ 1 year follow-up - 5 with syrinx	9.1 years§ (3–17)	Retrospective cohort, single center (phone survey in 06–07/2012)	Conservative	NA	2000–2001	5.1 years§ (1–11)	Clinical Surgery
Whitson et al. (2015)	52 asymptomatic CM1 - 0 with syrinx	8.2 years (2–16)	Prospective cohort, single center	Conservative	NA	12/2004–05/2013	NR (7–12 years)	Clinical MRI Surgery
Pomeraniec et al. (2016)	22 asymptomatic out of 70 conservatively managed CM1 - 2 with syrinx 3 asymptomatic out of 25 surgically treated CM1 - 16 with syrinx	8.3 years (1–18)	Retrospective cohort, single center, single surgeon	Conservative	Surgically treated symptomatic CM1 children	2004–2013	Clinically 66.3 months (0–9) By MRI 44.8 months (0–16)	Clinical MRI Surgery

Table 1 (continued)

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Leon et al. (2019)	427 asymptomatic and mildly symptomatic CM1 without syrinx (from the initial pool ($n = 698$), 254 (36.4%) were excluded for lack of follow-up). 44/427 excluded from multivariate model for missing info/variables	8.4 years§ (NR)	Retrospective cohort, single center	Conservative	NA	06/1996–12/2016	2.0 years** "surgery free" (0–15)§	Clinical MRI Surgery

*Cases probably overlap in the two studies, Novegno et al. is a subset of a cohort of 96 CM1

§Info available for the entire cohort, not for the subset considered

**Median value

Mildly symptomatic patients were not recommended for surgery

CM1, Chiari malformation, type 1; *MRI*, magnetic resonance imaging; *NA*, not applicable; *NR*, not reported

Andersen and coworkers' study [22]. The authors aimed to study the effect of bone decompression on auditory evoked potentials of the intraoperative Brainstem Auditory Evoked Potentials (BAEP) as an indicator of the effectiveness of bone decompression even without duraplasty; it is not clear, however, whether improvement in BAEPs can be considered a good indicator of subsequent postoperative clinical improvement [22].

Regarding the other three series of pediatric cases [1, 3, 23], two reported the long-term clinical and radiological outcomes of a large number of operated CM1 children suffering from various pathologies in association with CM1 [1, 3].

The goals of surgical management include the improvement of clinical symptoms, the ascent of the cerebellar tonsillar ectopia, and, if present, the reduction of Syr, by relieving pressure on the brainstem and restoring CSF flow. In symptomatic CM1 children, with or without Syr, surgery is indicated as being effective in almost all children, and sufficiently safe as it lacks a high complication rate [1, 3].

No study compared surgical treatment versus conservative management in symptomatic CM1 children, but Pomeraniec et al. reviewed 95 children of which 25 were surgically managed [13]. The authors reported that surgery was associated with better clinical and radiological outcomes: symptoms improved in 41.7% of conservatively managed patients and in 75% of surgically treated ones; in the conservative group, neither of the two patients with Syr showed syrinx improvement and three patients (4.3%) developed new Syr, whereas 87.5% of 16 surgically treated children showed improvement or resolution of the Syr. The authors concluded that appropriately selected symptomatic patients and those with Syr should be surgical candidates because of the high rates of clinical and radiological improvement.

Some studies aimed to identify clinical and/or neuroradiological risk factors in CM1 children as the limited understanding of the progression and of risk factors increases the ambiguity of defining surgical indications. Some clinical factors, unlike radiological characteristics, have proved to be of predictive value: an increased risk of significant neurological symptoms was observed in older children [15]; older age at diagnosis was also predictive of headache onset [15], while younger age predicted both improvement in symptoms [19] and Syr changes (improvement or worsening) [17]. Again, in the follow-up, an age inferior to 6 years old correlated to a risk of increased tonsillar ectopia, but the age between 6 and 18 years correlated to a reduction of tonsillar ectopia [16]. Regarding symptoms, the presence of cough-headache was a significant negative predictor of symptom improvement, whereas non-tussive headaches were a positive predictor for clinical improvement [19]. In addition, patients with a symptom duration of less than 2 years seem to have better outcomes after surgery [3].

Table 2 Characteristics of the included studies for PICO 2

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Anderson et al. (2003)	11 symptomatic CM1 - 6 (54.5%) with syrinx	9.8 years (3–19)	Prospective cohort, single center, single surgeon	11 PFDD	NA	11/2000–12/2001	12 months (6–19)	Neurophysiology
Tubbs et al. (2003)*	130 symptomatic CM1 14 (11%) with hydrocephalus 75 (58%) with syrinx	11 years (0.2–20)	Retrospective cohort, two centers, single surgeon	130 PFDD	NA	1979–2002	4.2 years (0.3–15)	Clinical MRI Surgery
Novegno et al. (2008)	11 mildly symptomatic CM1 (50% of 22 CM1 children) - 0 with syrinx - 1 with ventriculomegaly	7.2 years (2–16)	Retrospective cohort, single center	Conservative	NA	01/1988–11/2007	5.3 years (3–10)	Clinical MRI Surgery
Aitken et al. (2009)	32 mildly symptomatic CM1 (63% of 51 CM1 children) - 4 with syrinx	11 years§ (NR)	Retrospective cohort, multicenter	Conservative	NA	01/1997–12/1998	6.4 years§ (NR)	Clinical MRI Surgery
Benglis et al. (2011)	14 mildly symptomatic (11% of 124 CM1 children) - 2 with syrinx	7.0 years§ (0.9–19.8)	Retrospective cohort, single center	Conservative	NA	07/1999–07/2008	2.8 years§ (1.0–8.6)	Clinical MRI Surgery
Tubbs et al. (2011)*	500 symptomatic CM1 - 285 (57%) with syrinx - 48 (9.6%) with hydrocephalus	11 years (0.2–20)	Retrospective cohort, single center	500 PFDD	NA	1989–2010	5 years (0.2–15)	Clinical MRI Surgery
Pomeraniec et al. (2016)	48 symptomatic CM1 out 70 conservatively managed 22 symptomatic CM1 out of 25 surgically treated for clinical symptoms in 22 (88%), syrinx in 3 (%) - 16 (64%) with syrinx	8 years (0.9–18)	Retrospective cohort, single center, single surgeon	48 Conservative	11 PFDD 14 PFDO	2004–2013	Clinically 66.3 months (0–9) By MRI 44.8 months (0–16)	Clinical MRI
Knerlich-Lukoschus et al. (2019)	22 symptomatic CM1 with at least 3 months clinical and imaging follow-up	13 years (NR)	Retrospective cohort, single center	21 PFDO	NA	2015–2018	NR	Clinical MRI Surgery

*Tubbs 2003 had a major overlap with Tubbs 2011, but we were not able to separate the useful subset

§Data for the entire cohort, not for the subset considered

CM1, Chiari malformation, type 1; *MRI*, magnetic resonance imaging; *NA*, not applicable; *NR*, not reported; *PFDO*, posterior fossa decompression only; *PFDD*, posterior fossa decompression with duraplasty

In contrast, none of the radiological characteristics, including initial degree of tonsillar ectopia, tonsillar morphology, CSF flow at the foramen magnum, seems to be predictive of headache, significant neurologic symptoms development, the need for future surgery or postoperative resolution [1, 15, 17, 20].

More recently (after May 29, 2019), one review and three case series on the natural history of CM1 children have been published [24–27]. These studies came to largely overlapping conclusions: within 6 months of the first visit, 10–15% of CM1 children require surgery, in most cases due to the presence of Syr which seems the only statistically significant factor for the need for surgery [26, 27]; however, children not treated surgically at the time of diagnosis are unlikely to require surgery over time. Indeed, the evolution of CM1 was benign in most cases with the development of new symptoms or new syrinx in a smaller subgroup (from 6.4 to 7.2%) of asymptomatic or incidentally diagnosed initially managed conservatively children [26, 27].

PICO 3: For children with CM1 selected for surgery, without associated malformations, is bone cranio-vertebral decompression the most effective intervention?

The literature search found 22 papers satisfying our inclusion criteria: one RCT [28], 19 retrospective cohort studies [29–49], and two systematic reviews with meta-analysis [50, 51], all focusing on the comparison between posterior fossa decompression with bone decompression only (PFDO) and PFD with duraplasty (PFDD). The systematic reviews reported on nine of the 19 cohort papers. The description of the included studies is presented in Table 3 and their quality evaluation is reported in Appendix 3 Tables 10 and 11 [11]. Findings on each outcome measure are summarized in Table 4.

Duration of surgery was reported in 2/19 cohort studies. The mean duration was 105 min for the 63 children treated with PFDO versus (vs) 169 min for those treated with PFDD ($n=47$) in the study by Litvak et al. [35]; it was 90 min in the 29 children treated with PFDO vs 148 min in the 36 children treated with PFDD in the study by Lee A et al. [38].

Figures were 119 min for 45 PFDO vs 166 min for 45 PFDD in the RCT [28].

The mean length of stay (reported in 7/19 studies) was between 2 [44] and 4 days [30] for PFDO; it was between 3 [38] and 7 days [43] for PFDD. In the RCT, the mean length of stay was 8 (PFDO) vs 10 days (PFDD) [28] (Table 4).

Surgical complications were reported in 13/19 cohort studies for PFDO; eight studies (62%) had < 5% surgical complications [30, 32, 35, 40, 42, 43, 46, 48]; two studies (15%) had 5–10% complications [29, 44], and three studies (23%) had 11–20% complications [38, 45, 49]. Figures for PFDD were from 14 studies: two studies (14%) with < 5% surgical complications [32, 42], seven studies (50%) with 11–20% complications [30, 35, 39, 40, 45, 46, 49], and five studies (36%) with > 20% complications [29, 38, 43, 44, 48]. The RCT found surgical complications in 12.5% of PFDO and in 57.1% of PFDD; no significant between-group difference in bleedings was reported [28] (Table 4).

Revision surgery was reported in 10/19 cohort studies. In PFDO-treated patients, it was needed in 0% of children in nine of the studies [29, 30, 35, 38, 40, 43, 44, 48, 49] and in 0.7% of children in one study [42]. Figures for PFDD-treated children ranged between 2% [35] and 19% [29]. The RCT reported 0% revision surgery for both procedures [28] (Table 4).

Overall improvement data were reported in 14/19 cohort studies. The data were presented as percentages (10 studies), change in scale values (3 studies), and report (1 study). The RCT reported this outcome with the Chicago Chiari Outcome Scale (CCOS) [28]. For one study with a scale value, a transformation in percentage was possible [49].

Overall improvement for PFDO ranged from 47% [31] to 100% [33, 47], and was ≥ 90% in 5/11 studies. For PFDD, figures ranged from 64% [44] to 100% [33, 47]; 4/11 studies reported an improvement ≥ 90%.

Three children out 4 improved after PFDO, and 3/3 after PFDD in one study on CM1 with sleep apneas [41]. Two cohort studies [38, 43] and the RCT [28] reported no difference between the two surgical techniques on the CCOS score (Table 4).

All the 20 studies had a subgroup of CM1 with syrinx, but only seven reported data on syrinx improvement for the two surgical procedures. For PFDO, improvement ranged from 40% [33] to 100% [38]; syrinx improvement was ≥ 80% in 3/7 studies. For PFDD, it ranged from 60% [44] to 100% [33] and syrinx improvement was ≥ 80% in 6/7 studies. No statistical difference on this outcome was found in five studies reporting on 53 PFDO and 139 PFDD [33, 38, 40, 43, 44], and it was commented as "no difference in percentage" in 70 Syr with the two surgical approaches [49] or no analyzed/commented in 6 PFDO (66.7% improved) vs 20 PFDD (85% improved) [30]. In the RCT, figures were 82.5% (PFDO) vs 90.5% (PFDD) and the difference was not statistically significant [28] (Table 4).

The reoperation rate was reported in 14/19 cohort studies for PFDO: it was < 5% in two of the studies [35, 43]; 5–10% in five studies [30, 32, 40, 44, 47]; 11–20% in three studies [29, 33, 48]; > 20% in four studies [41, 45, 46, 49]. It was reported in 13 cohort studies for PFDD: it was < 5% in four studies [30, 33, 35, 47]; 5–10% in four studies [32, 43, 45, 48]; 11–20% in three studies [29, 40, 49]; > 20% in two studies [41, 46].

Only four studies reported statistical analysis, with no statistical difference for the two groups [35, 46, 48, 49]. The RCT did not report on this outcome [28].

Table 3 Characteristics of the included studies for PICO 3

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Jiang et al. (2018)	90 symptomatic/ asymptomatic CM1 (100% with syrinx; 76.8% or 81.7%[#] had scoliosis)	NR (10–18 years)	**RCT** single blind, single center	45 PFDO	45 PFDD	10/2011–06/2015	NR (≥ 24 months)	CCOM scale for four domains MRI Surgical complications
Navarro et al. (2004)	96 symptomatic CM1 (41 with syrinx)	NR (0.5–18 years)	Retrospective cohort, single center	63 PFDO (21 syrinx)	33 PFDD (21 syrinx)	1989–2001	2.3 years (0.17– 9.8)	Clinical outcome (dicotomic)
Yeh et al. (2006)	130 symptomatic CM1 with ultrasonography during surgery (125 analyzed)	5.9 years§ (0.9–18)	Retrospective cohort, single center	40 PFDO (6 syrinx)	85 PFDD (20 syrinx)	1995–2003	20 months§ (NR)	Length of stay MRI Surgical complications
Galarza et al. (2007)	60 symptomatic CM1 (24 with syrinx)	10 years (1–18)	Retrospective cohort, single center	19 PFDO	41 PFDD (19 tonsillar resection)	1997–2002	21 months (1–10 years)	Clinical MRI (42% of syrinx lost to follow-up)
McGirt et al. (2008)	256 symptomatic CM1 with ultrasonography during surgery	10 years (NR)	Retrospective cohort, single center	116 PFDO (9 syrinx)	140 PFDD (60 syrinx)	1995–2005	29 months (NR)	Persistence or recurrence of symptoms
Shamij et al. (2010) Venturyra et al. (2003) §§	24/29 symptomatic CM1 with pre-surgery Cine MRI	NR (1.5–18 years)	Retrospective cohort, single center	17 PFDO (5 syrinx)	7 PFDD (5 syrinx)	01/1990–03/2006	NR (at least 6 months)	Clinical MRI Electrophysiology
Litvack et al. (2013) Limonadi et a. (2004) §§§	110 symptomatic CM1 children	8.3 years PFD 10.4 PFDD (NR)	Retrospective cohort, single center, single surgeon	63 PFDO (5 syrinx)	47 PFDD (44 syrinx)	01/2000–03/2009	16 months (NR)	Clinical Surgical complications Resource utilization
Chotai et al. (2014)	6/42 CM1, age 16–20 years (36 were adults)	NR	Retrospective cohort, single center	5 PFDO (no syrinx)	1 PFDD (no syrinx)	NR	NR	Clinical
Lee A et al. (2014)	65 consecutive symptomatic CM1	9.5 years (NR)	Retrospective cohort, single center	29 PFDO (8 syrinx)	36 PFDD (15 syrinx)	07/2003–03/2011	23.6 months (NR)	CCOS MRI Surgical complications
Lee S et al. (2014)	56 symptomatic CM1, ≥ 1 year follow-up	7.9 years (0.1–17)	Retrospective cohort, single center	*9 other techniques*	46 PFDD (37 syrinx)	1991–2010	75.9 months (12–173)	Clinical MRI Surgical [outcomes data available only for 37 pts with syrinx]

Table 3 (continued)

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Narenthiran et al. (2015)	19 symptomatic CM1 (2 with scoliosis only) with intraoperative ultrasound scan	10.5 years (2–17)	Retrospective cohort, single center	11 PFDO (7 syrinx)	8 dura opening without duraplasty (7 syrinx)	06/2011–12/2012	1 year (NR)	Clinical MRI Surgical complications/redo
Pomeraniec et al. (2015)	7/8 CM1 with central sleep apnea	11.9 years (2.2–17.1)	Retrospective cohort, single center	4 PFDO (1 syrinx)	3 PFDD (1 syrinx)	2004–2014	Clinical 47.4** (3.2–98.3) Radiological 45.7** months (3.2–107.4)	Clinical MRI (CSF flow) Surgical complications/redo
Shweikeh et al. (2015)	2649 CM1 Kids' Inpatient Database (KID), US representative	10.3 years (0–20)	Retrospective cohort, multicenter	1593 PFDO (16.8% syrinx)	1056 PFDD (24.8% syrinx)	2000–2009	NA	Revision surgery Complications Non-routine discharge
Gallo et al. (2017)	46 consecutive CM1	11.9 years (NR)	Retrospective cohort, single center	17 PFDO (5 syrinx)	17 PFDD + 17 dura opening (13 + 13 syrinx)	01/2008–12/2014	46 months** (16–98)	CCOS MRI Surgical complications/redo
Pisapia et al. (2017)	189 CM1 aged < 22 years	10 years** (NR)	Retrospective cohort, single center	98 PFDO (22 syrinx)	91 PFDD (66 syrinx)	2004–2014	2 months** (1–75)	CSI MRI Surgical complications/redo
Raza Knight et al. (2017)	96 symptomatic CM1 (63 with syrinx)	8.7 years (NR)	Retrospective cohort, single center	26 PFDO	70 PFDD	1989–2014	NR (at least 1 year)	Clinical (for 57 with headache only) Surgery
Grahovac et al. (2018) §§§§	16 symptomatic CM1 (1 syrinx)	20.7 months (5–35)	Retrospective cohort, single center	10 PFDO	6 PFDD	06/2007–11/2014	5.6 years (3–10)	Clinical MRI Surgery
Entezami et al. (2019)	33 CM1 with surgery (14 with syrinx)/132 CM1 cohort	10.5 years § (0.6–18)	Retrospective cohort, single center, single surgeon	12 PFDO	21 PFDD	2009–2015	1.3 years §	Clinical Surgery
Gernsback-Tomita et al. (2019) §§§	61 CM1	8.9 years (NR)	Retrospective cohort, single center, single surgeon	25 PFDO (4 syrinx)	36 PFDD (25 syrinx)	2007–2017	NR	Surgical complications/redo
Walker-Palmer et al. (2019)	70 symptomatic children (52 with syrinx)	11 years** (2.5–17.2)	Retrospective cohort, single center	14 PFDO	56 PFDD (39 with tonsillar resection)	1982–2015	63.9 months (4.6–240)	CCOS MRI Surgery

Table 3 (continued)

[#]Numbers are different between text and tables

[**]Median value

[§]For the entire cohort

[§§]Shamji 2010 is an update of Venturyra 2003

[§§§]Litvack 2013 is the update of Limonadi 2004

[§§§§]Probable overlap between the two populations but we were unable to separate them

CM1, Chiari malformation, type 1; *RCT*, randomized controlled trial; *PFDO*, posterior fossa decompression only; *PFDD*, posterior fossa decompression with duraplasty; *CCOS*, Chicago Chiari Outcome Scale; *MRI*, magnetic resonance imaging; *NA*, not applicable; *NR*, not reported; *CSF*, cerebro-spinal fluid; *CSI*, Chiari Severity Index

Commentary

The choice of the best surgical treatment of CM1 children without associated malformations is challenging and not clear at the state of art.

We focused on comparing PFDO and PFDD, with or without tonsillar resection. PFDD, a more aggressive choice, is associated with longer surgery and hospitalization times and higher complication rates. Consequently, some authors have suggested the use of ultrasound to optimize the surgical strategy avoiding unnecessary maneuvers and ensuring sufficient decompression [29, 32, 33, 40, 48]; however, the evidence to support this advice is weak (level 4 of evidence).

Concerning Syr, PFDD seems not advantageous over PFDO. Revision surgery comparison for the two techniques was not statistically significant in 3/4 studies [28, 35, 38]; the US KID database reported a $p = 0.01$ favoring PFDO, when comparing 1593 PFDO vs 1056 PFDD [42]. Considering the overall clinical improvement, one review [51] reported PFDD superiority, but all the included studies using a validated scale for clinical outcome reported no differences [28, 38, 43, 49]. In our report, overall improvement was not significant in 8/9 studies. It was $p = 0.05$ and favored PFDD only in one [31]. One study reported a multivariate model analyzing symptom-free survival and adjusting for all variables differing between the two groups: PFDO was associated with a twofold increased risk of symptom recurrence only in children with tonsillar herniation caudal to C1 ($p = 0.034$), proposing the concept of specific subgroup tailored surgery [32].

In the literature for surgery in the CM1 children population, we found no homogeneity in recruitment criteria. Methodology varied substantially between studies and also the radiological definition of CM1 was not homogenous. Clinical outcomes evaluation was frequently difficult to compare across studies. The timing for reporting the selected outcomes was extremely variable and not consistent among studies. The statistical analysis was done on population samples too small for appropriate analysis with stratifications or adjusting for confounders.

The two reviews on this topic underlined the low level of quality and the presence of several biases in the studies included in the meta-analysis [50, 51].

PICO 4. For children with CM1 and associated malformations (hydrocephalus or craniosynostosis or tethered cord), which is the most effective surgical approach?
PICO 5. For CM1 children with cranio-vertebral junction malformation, is cranio-vertebral decompression more effective than other surgical approaches?

The management of some diseases associated with CM1 is controversial because of the still unclear pathogenesis and

Table 4 Main findings of the included studies for PICO 3

Surgical procedure	Study	N. of children	Mean length of surgery / stay	% Surgical complications	% Revision surgery	% Overall improvement	% Syrinx improvement	% Reoperation rate
	Jiang et al. (2018) (RCT)	45	119 min / 8 days §	12.5 §	0	15.30*	82.5	-
PFDO	Navarro et al. (2004)	56	-	6.3 §§	0	72.2	NR	12.7
	Yeh et al. (2006)	40	4.3 days §	0.0	0	90.0	66.7	10.0
	Galarza et al. (2007)	19	-	Mixed data	Mixed data	47.4	Mixed data	
	McGirt et al. (2008)	116	4 days	0.9	NR	Mixed data	NR	7.8
	Shamij et al. (2010)	17	-	NR	NR	100	40 (2/5)	17.6
	Litvack et al. (2013)	63	105.5 min §	3.2	0.0	90.0	NR	1.6
	Chotai et al. (2014)	5	A subset of a larger study on adults; 16–20 years was the first class					
	Lee A et al. (2014)	29	90 min / 2.1 days §	10.3	0.0	14.6*	100	NR
	Lee S et al. (2014)	1	-	NR	NR	NR	NR	NR
	Narenthiran et al. (2015)	11	-	0.0	0.0	63.6	71.4	9.1
	Pomeraniec et al. (2015)	4	3.5 days**	Mixed data	-	75.0	100 (1/1)	25.0 (1/4)
	Shweikeh et al. (2015)	1593	3.8 days §	0.8 §§	0.7 §§	-	-	-
	Gallo et al. (2017)	17	4 days §	0.0 §§	0.0	14.6*	80.0	0.0
	Pisapia et al. (2017)	98	2 days §§	5.1 §	0.0	58.0	60.0	8.0
	Raza Knight et al. (2017)	26	-	11.5	NR	56.3 (headache)	NR	53.8
	Grahovac et al. (2018) (a)	10	-	0.0	-	60.0	-	50.0
	Entezami et al. (2019)	12	-	NR	NR	100	Mixed data	8.3
	Gernsback-Tomita et al. (2019) (a)	25	-	0.0	0.0	Mixed data	Mixed data	20.0
	Walker-Palmer et al. (2019)	14	-	14.3	0.0	14.0* (93.0)	85.7	28.6

Table 4 (continued)

Surgical procedure	Study	N. of children	Mean length of surgery / stay	% Surgical complications	% Revision surgery	% Overall improvement	% Syrinx improvement	% Reoperation rate
PFDD	Jiang et al. (2018) (RCT)	45	166 min / 10 days	57.1	0.0	15.1*	90.5	-
	Navarro et al. (2004)	53	-	46.9	18.8	68.4	NR	15.6
	Yeh et al. (2006)	85	6.4 days	13.3	5.9	97.6	85.0	2.4
	Galarza et al. (2007)	41	-	Mixed data	mixed data	80.5	Mixed data	-
	McGirt et al. (2008)	140	4 days	3.6	NR	Mixed data	NR	7.1
	Shamij et al. (2010)	7	-	NR	NR	100	100	0.0
	Litvack et al. (2013)	47	168.9 min	12.8	2.1	91.4	NR	0.0
	Chotai et al. (2014)	1	A subset of a larger study on adults; 16–20 years was the first class					
	Lee A et al. (2014)	36	148 min / 3.3 days	22.2	11.0	14.7*	77.0	NR
	Lee S et al. (2014)	37	-	16.7	8.0	84.0	86.0	NR
	Narenthiran et al. (2015)	8	-	12.5	12.5	75.0	85.7	12.5
	Pomeraniec et al. (2015)	3	4 days**	Mixed data	-	100 (3/3)	100 (1/1)	66.7 (2/3)
	Shweikeh et al. (2015)	1056	4.4 days	2.3	2.1	-	-	-
	Gallo et al. (2017)	34	7 days	29.0	2.9	14.5	92.0	5.9
	Pisapia et al. (2017)	91	4 days	29.7	Mixed data	64.0	60.0	Mixed data
	Raza Knight et al. (2017)	70	-	11.4	NR	84.2 (headache)	NR	5.7
	Grahovac et al. (2018) (a)	6	-	16.7	-	83.3	-	33.3
	Entezami et al. (2019)	21	-	NR	NR	100	Mixed data	0.0
	Gernsback-Tomita et al. (2019) (a)	36	-	25.0	5.6	Mixed data	MIXED data	5.6
	Walker-Palmer et al. (2019)	56	-	19.6	8.9	13.7* (89.3)	86.7	16.0

*Mean CCOS (Chicago Chiari Outcome Scale) total score

**Median value

§ $= p \leq 0.001$

§§ $= p < 0.05$

(a) Probable overlap between the two populations but we were unable to separate them

PFDO, posterior fossa decompression only; *PFDD*, posterior fossa decompression with duraplasty; *NR*, not reported

for the difference in the therapeutic options adopted by the different centers. The review of the literature did not show any high level of evidence to support specific theories or strategies. No trials nor systematic reviews have been published so far.

Thirteen retrospective studies (level 4 of evidence) fulfilled the selection criteria (Tables 5 and 6). In four articles, the association between CM1 and craniosynostosis was analyzed [52–55]. One study pointed out some epidemiological data on such association in a series of 383 children treated for craniosynostosis [55]. 7.5% of patients (29 cases) showed CM1 mainly as a result of pansynostosis, lambdoid or multisutural synostosis, the presence of venous anomalies (28%), syndrome (45%), or hydrocephalus (52%) being the most important findings shared by the two conditions. In 13 cases, only the repair of the craniosynostosis was realized with good results on CM1. The simultaneous performance of craniosynostosis repair and suboccipital decompression was indicated as safe and effective in selected cases (syndromic and/or lambdoid synostosis) by another study [54]. On the other hand, foramen magnum decompression alone was found to be effective in improving significantly central sleep apneas in children with syndromic synostosis and CM1 [52]. The last study revealed that there is a predominance in the tonsillar descent to the synostotic suture side in asymmetric craniosynostosis cases [53].

Three papers concerned the association between CM1 and hydrocephalus [1, 3, 39]. Hydrocephalus was present in 11% of cases in the large series (130 cases) described by Tubbs and coworkers in 2003 [1] and in 9.6% of cases in the update (500 cases) provided in 2011 [3]. The correct functioning of CSF shunt was verified prior to suboccipital decompression of hydrocephalic patients. In the third study, children with hydrocephalus were grouped separately from those with CM1 alone or with syringomyelia [39]. In this subset of patients (8 cases), the hydrocephalus was treated first (CSF shunt) and only one patient required suboccipital decompression.

There was only one study addressing the association between CM1 and tethered cord [56]. The incidence of CM1 among 170 children who underwent spinal cord detethering was 10% (17 cases). All patients showed an improvement of their symptoms, which were considered related to tethered cord rather than CM1 (headache, lower extremity sensory disturbance, constipation, scoliosis, urinary incontinence, toe walking, etc.). No radiological modification of the tonsillar descent was obtained.

Finally, the study by Balestrino et al., who reported on 31 children with associated anomalies out of 172 pediatric CM1 (16 with hydrocephalus, 6 with craniosynostosis, and 9 with tethered cord), confirmed the attitude of treating the symptomatic associated condition first. Among them, 37.5% of hydrocephalic children, 50% of those with craniosynostosis, and 22.2% of those with tethered cord also required the foramen magnum decompression for their CM1 [57].

The last four studies reported on the association between CM1 and other CVJ anomalies [58–61]. The first study emphasized that a ventral compression of the brainstem is a common finding in CM1 children and young adults (48% and 28% out of 40 patients had flattening and distortion of the brainstem, respectively) but only a minority of them (5%) show a real basilar invagination [58]. A one-step treatment by means of suboccipital decompression and posterior fixation was proposed for the management of CM1 and basilar invagination based on a preliminary and successful experience on 11 children [59]. Basilar invagination, clival-axial angle < 125°, and Chiari 1.5 were found to be the main risk factors predicting the need for posterior fixation [60]. The last study investigated the possibility of successful treatment with atlanto-axial fixation not only CM1 children with basilar invagination but also those without manifest bone anomalies [61].

Commentary

Craniosynostosis

Maldevelopment of posterior fossa (PF), premature fusion of sutures and basal synchondroses, and comorbidities (e.g., venous hypertension, OSAS) account for an incidence of CM1 in syndromic synostosis as high as 80–100% [62]. An associated large foramen magnum (reduced A-P diameter but wide L-L diameter) would favor the tonsillar descent, while a small one (both A-P and L-L diameters reduced) would prevent it [63, 64]. Moreover, about 5–6% of children with isolated sagittal synostosis, 45–60% with lambdoid synostosis, and 60% with Mercedes-Benz synostosis harbor CM1 [65–68].

Since an etiologic treatment is suggested for CM1 whenever possible, the craniosynostosis is treated first [55]. The early recognition of unisutural synostosis is therefore mandatory to avoid management mistakes. The benefic effects on CM1 come from the PF expansion (direct decompression of the PF, improvement of possibly associated hydrocephalus) and/or from the anterior distraction (relief from raised intra-cranial pressure). Some authors proposed to maximize the bi-parieto-occipital expansion through a posterior vault distraction both in syndromic and non-syndromic uni- or bi-lambdoid synostoses [69] or even in CM1 subjects without craniosynostosis [70]. The latter proposal seems reasonable only in case of repeatedly failed foramen magnum osteodural decompression, also because of the high rate of complications (50%) [71].

A certain debate exists about the management of CM1 and Syr in children with a late diagnosis of craniosynostosis [54, 72, 73]. A reliable option is to address CM1 in case of

Table 5 Characteristics of the included studies for PICO 4

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Tubbs et al. (2003)*	14 CM1 with hydrocephalus out of 130 symptomatic CM1 patients	11 years (0.2–20)	Retrospective cohort, two centers, single surgeon	NA	NA	1979–2002	NR	Clinical MRI Surgery
Tubbs et al. (2011)*	48 CM1 with hydrocephalus out of 500 symptomatic CM1 patients	11 years (0.2–20)	Retrospective cohort, single center	NA	NA	1989–2010	5 years (0.2–15)	Clinical MRI Surgery
Strahle et al. (2011) bis	17 CM1 with craniosynostosis	1.8 years (0.2–9)	Retrospective cohort, single center	NA	NA	1994–2009	NR	MRI
Karppinen et al. (2012)	11 CM1 with non-syndromic single-suture craniosynostosis (asymptomatic for CM1)	44 months (NR)	Retrospective cohort, single center	NA	NA	01/2004–10/2010	NA (immediate post–surgery)	MRI
Addo et al. (2013)	5 CM1 with craniosynostosis and central sleep apnea	4.1 years** (1.1–12.6)	Retrospective cohort, single center	NA	NA	12/2007–12/2009	3.6 years** (NR)	Clinical MRI Surgery
Scott et al. (2013)	34 CM1 with craniosynostosis	23.6 months (10–108)	Retrospective cohort, single center	NA	NA	1995–2011	3.8 years (0.5–14)	Clinical MRI Surgery
Lee S et al. (2014)	8 CM1 with hydrocephalus out of 56 symptomatic CM1	7.9 years§ (0.1–17)	Retrospective cohort, single center	NA	NA	1991–2010	75.9 months§ (12–173)	Surgery
Glenn et al. (2015)	17 CM1 with tethered cord syndrome	7 years (1.5–15.7)	Retrospective cohort, single center	NA	NA	2008–2012	21.3 months (NR)	Clinical MRI
Balestrino et al. (2019)	16 CM1 with hydrocephalus, 6 with craniosynostosis, 9 with tethered cord out of 172 treated patients	8.1 years (0.4–19)§	Retrospective cohort, single center	NA	NA	2006–2017	5.1 years (0.2–10.9)§	Surgery

*Tubbs 2011 had major overlap with Tubbs 2003 but we were not able to separate the useful subset

**Median value

§For the entire cohort

CM1, Chiari malformation, type 1; *MRI*, magnetic resonance imaging; *NA*, not applicable; *NR*, not reported

specific symptoms/syringomyelia and the synostosis in case of raised intra-cranial pressure (ICP) [74, 75]. ICP monitoring may be useful in selected cases [76]. Further help will come in the future from the genetic assessment [77].

Table 6 Characteristics of the included studies for PICO 5

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Grabb et al. (1999)	38 patients < 18 years/40 reported	8.6 years § (1.3–27.4)	Retrospective cohort, single center	NA	NA	NR (3 year period)	NR	Radiology-based anatomical study
Kim et al. (2004)	11 CM1 and BI (not based on the Wackenheim clival-canal line)	8.7 years (1.5–17)	Retrospective cohort, single center	NA	NA	01/1994–05/2002	39.4 months (3–92)	Clinical Surgical complications
Bollo et al. (2012)	101 CM1/206 treated (MRI pre and post-surgery available) 82 suboccipital decompression alone, 19 occipito-cervical fusion	9.1 years (0.7–21.9)	Retrospective cohort, single center	NA	NA	1995–2010	2.3 years (0.1–9.3)	Risk factors for need for occipito-cervical fusion
Goel et al. (2018)	24 CM1 with basilar invagination (9 with syrinx) /33 children	NR (0.9–18 years)§	Retrospective cohort, single center	NA	NA	01/2010–07/2017	33 months§ (3–78)	Clinical: JOA score Goel's Clinical Grade VAS

§For the entire cohort

CM1, Chiari malformation, type 1; *MRI*, magnetic resonance imaging; *NA*, not applicable; *NR*, not reported; *BI*, basilar invagination; *JOA*, Japanese Orthopedic Association Grading Scale; *VAS*, visual analog score

Hydrocephalus

The pathogenesis of the primary association between CM1 and hydrocephalus remains partially obscure. The tonsillar herniation resulting from raised ICP due to hydrocephalus is just transient and reversible (not CM1) [78], while the venous engorgement resulting from the hypoplasic posterior fossa and the occlusion of the jugular foramina can justify both CM1 (due to cerebellar edema) and hydrocephalus (due to CSF hypo-resorption) in syndromic patients [79]. In non-syndromic CM1 children, hydrocephalus would result from occlusion of the basal CSF pathways, which would be complete in a minority of patients (only 7–10% of CM1 subjects develop hydrocephalus), while it would be partial in the remaining cases (no hydrocephalus) [80–82].

Hydrocephalus complicates the management of CM1 and prolongs the hospital stay [83]. Because of its "obstructive" genesis, endoscopic third ventriculostomy (ETV) is regarded as the best therapeutic option, providing a high rate of success on hydrocephalus (90.5% of cases), CM1 (78.5% and 74% of clinical and radiological resolution, respectively), and syringomyelia (76% and 89%) [80]. Only 11% of patients require a treatment for persisting CM1 after ETV because of significant PF hypoplasia [84, 85]. Hydrocephalus should be treated first because more symptomatic, to reduce the risk of complications of raised ICP after PF decompression and because of the low rate of persisting CM1 symptoms after ETV. Favorable outcomes with PF decompression and successful evolution of the hydrocephalus are reported, especially in the case of ventriculomegaly (that is without raised ICP) [86].

Tethered cord

An "evident" tethered cord syndrome is sporadically associated with CM1 (up to 6–10% in selected series, < 1% in the clinical practice) [87, 88]. The spinal cord detethering improves the not related-CM1 symptoms [56]. Should typical CM1 symptoms be present too, both CM1 and tethered cord have to be surgically addressed, starting from the most symptomatic one, in separate stages [87, 89] or concurrently [90].

A relevant debate is around occult tethered cord syndrome (OTCS) and CM1. OTCS is defined as a symptomatic condition associated with normal appearance and position of conus and filum on MRI. Some studies showing a fibrous composition of an apparently normal filum or its abnormally posterior position in prone MRI, and improvement of urologic symptoms after filum sectioning, support this definition [91–93]. A first controversy concerns the too general criteria for OCTS definition and evolution, and the similar outcome of medical treatment and filum section on randomized studies [94]. A second controversy is on the caudal traction theory, which is advocated to explain the

association among CM1, CVJ anomalies, Syr, and scoliosis (neuro-cranio-vertebral syndrome), which would be a continuum with occult tethered cord (filum disease) and which would benefit from the extradural filum section [95, 96]. The sporadic and late occurrence of CM1 in children with tethered cord [97] and the tonsillar ascent after filum section in isolated cases support this theory [89, 98, 99]. However, the scientific impact of some of these studies is poor. Moreover, there is no evidence of changed position of the tonsils after spinal cord detethering in large series [56, 100, 101]. Clinical and experimental studies are against the caudal traction theory, showing normal course of the thoraco-lumbar roots (no CM1 in experimental models of tethered cord, no tonsils movement in case of caudal spinal cord traction in cadaveric models, no correlation between conus position and presence/severity of CM1) [102]. Some anatomical findings (fusion of the filum at the level or above S1 in about one-third of cases and off the midline in 11% of cases) question the effectiveness of extradural section of the filum [103, 104]. The absence of small posterior fossa in patients with tethered cord [105] prompted some authors to the preliminary identification of a subpopulation of CM1 subjects (normal PF, low lying tonsils, associated OTCS) that could benefit from filum section [106]. To date, however, there is no evidence to consider occult tethered cord as CM1 comorbidity and to promote the filum section in CM1 [100, 107–109].

CVJ abnormalities

CM1 associated with CVJ anomalies configures the so-called complex CM1 [110]. This condition could be the result of a primary mesodermal development defect leading to invagination of the odontoid (basilar invagination) or an acquired process due to softening of the skull (basilar impression) or rheumatoid arthritis (cranial settling), coupled with PF hypoplasia [111, 112], or the consequences of atlanto-axial instability. The definition of the latter is not universally accepted yet [113–115]. The management of complex CM1 has been traditionally based on the suboccipital decompression alone (in case of mild ventral compression) or the ventral decompression (in case of significant basilar invagination) plus suboccipital decompression (if required) and occipito-cervical stabilization (in case of instability) [116–118]. The experience with large series shows that ventral decompression is required only in a minority of cases [119]. The knowledge of anatomy and age-related morphometric measures is mandatory in children [120]. Accordingly, some authors have proposed personal management algorithms based on anatomical landmarks (e.g., the clival-axial angle and the basion-C2 distance) [121].

Some authors have raised a debate by indicating the central atlanto-axial instability as a common precursor for CVJ anomalies, including CM1 [122, 123]. This hypothesis concerns both an evident instability and a "microinstability" (absence of radiological signs of instability but intraoperative findings at facet atlanto-axial joints pointing that). Accordingly, the posterior C1-C2 fusion has been used as a unique, standard approach for all CVJ anomalies, with reported good results [124–126]. However, despite the effectiveness of C1-C2 stabilization in selected cases, its results are not better than suboccipital decompression in CM1 subjects and C1-C2 fusion is not advisable in case of significant bleeding from paravertebral venous plexus, gross C1-2 rotation, or vertical C1-2 joints with unilateral C1 or C2 facet hypoplasia, maldevelopment of the lateral masses and facet joints, very young age, unfavorable course of the vertebral artery [127, 128]. According to a recent meta-analysis of the literature, there is no evidence to support the atlanto-axial instability theory and the C1-C2 surgical strategy [129].

The need to look for instability in every CM1 case is another controversial topic [100]. The misdiagnosis of basilar invagination or atlanto-axial dislocation in CM1 patients is burdened by a high risk of failed suboccipital decompression and challenging revision (fixation) surgery [130]. Therefore, a careful preoperative work-up seems to be recommended in CM1 children, where some findings, like the retroverted dens (81–84%), are very common [131, 132]. The diagnostic and therapeutic approach must be tailored to the type of abnormality and the patient's age [133].

PICO 6: For children with failed CM1 surgery, is early redo surgery (≤ 12 months) more effective than late redo (> 12 months) or no surgery?

From 460 screened papers, we identified two cohort studies (Table 7).

Kennedy et al. reported a series of 156 children including 44% with associated syringomyelia, who underwent PFDO as their first surgery [134]. PFDO failed in 14 (9%) children, at a mean time of 22 months. The criteria for reoperation were "persistent, recurrent, or new CM1 symptoms" or progression of scoliosis without improvement of Syr. The tonsils descent below C2 and associated Syr were risk factors for reoperation. A more aggressive surgery, such as PFDD with or without tonsils coagulation, was performed in 11/14. In the second paper, Tubbs and coworkers reported a small series (8 children) of PFDO failures due to arachnoid veil and Magendie occlusion, and suggested posterior fossa re-exploration in case of Syr not responding to surgery [135].

Commentary

Despite the relevance of the problem, evidence on failed CM1 surgery is lacking. All together the included studies report 22 reoperated children, a too low number to draw definitive conclusions. Moreover, populations are different:

Table 7 Characteristics of the included studies for PICO 6

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Tubbs et al. (2004)	8 reoperated for persistent syringomyelia following CM1 PFDO	12.0 years (9–18)	Retrospective cohort, single center	NA	NA	NR	1.3 years (1–3)	MRI Surgical
Kennedy et al. (2015)	14/152 consecutive CM1 PFDO without dural opening, reoperated due to persistent symptoms and/or syrinx	9.9 years (0.5–20.6)§	Retrospective cohort, single center	NA	NA	2003–2013	32 months§ (NR)	Clinical MRI Surgical

§Info available for the entire cohort, not for the 14 reoperated

CM1, Chiari malformation, type 1; *PFDO*, posterior fossa decompression only; *MRI*, magnetic resonance imaging; *NA*, not applicable; *NR*, not reported

Kennedy et al. reported the results of a "mininvasive" approach on mildly symptomatic children. For these children submitted to PFDO, an upgrade surgery seems enough [134].

Sacco and Scott reported a series of 16 reoperations. CM1 and CM2 were included, as well as CM1 with associated malformations. This paper, with mixed population and no data on the time and type of first surgery, still needs some comments: the authors identified younger age (< 5 years) and associated craniosynostosis as risk factors for surgical failure, and add fourth ventricle stenting as surgical option for reoperations [136].

Tubbs et al. and Sacco and Scott deal with more aggressive approaches and both indicate posterior fossa arachnoiditis as a possible cause of failure, suggesting different reoperation techniques (stenting versus adhesiolysis) [135, 136].

In conclusion, due to the low numbers, different types of surgery, and different inclusion criteria, none of the included papers was able to indicate the correct timing for CM1 postoperative follow-up, the criteria to indicate reintervention, and the type of redo surgery. A correct pathway still needs to be processed.

PICO 7: For children with syringomyelia without CM1, which is the most effective clinical, radiological, and surgical planning?

Syr without CM1 is a rare occurrence and recognizes disparate causes as spinal tumors, vascular malformations, tethered cord, cysts, and arachnoiditis due to previous infections, hemorrhages, and/or traumas. In all these cases, Syr is defined as secondary Syr without CM1 [137]. Once all the possible known causes are excluded, the literature defines Syr without CM1 as isolated Syr [137].

Of 376 identified references concerning Syr without CM1, 19 articles were evaluated as full papers and five were included: one RCT and four cohort studies (Fig. 2).

The RCT included 30 children with terminal Syr due to tethered cord [138], sixteen children were randomly assigned to spinal cord untethering and 14 children to untethering plus syrinx drainage. The differences for improvement rates of sensory deficits and urinary disfunction were statistically significant ($p = 0.036$ and $p = 0.05$, respectively) in favor of the combined procedure.

Lee JY et al. retrospectively reviewed a uniform group of 33 patients with preoperative syringomyelia associated with tethered cord and treated by untethering alone. After surgery, 31 of 32 patients (97%) showed long-term stability (mean follow-up 36 months) or a decrease in the syrinx measures. Only in one patient with retethering the syrinx increased and new urinary symptoms appeared. The authors concluded that untethering alone may be sufficient for the management of syringomyelia associated with tethered cord [139].

Three retrospective case series concerned isolated Syr followed for a mean time ranging between 16 and 24 months [137, 140, 141]. Magge et al. reported a good natural course in 32 children, with 91% of stabilization or improvement [137]; Joseph et al. confirmed the good outcome with no neurological deterioration neither Syr increase in all 39 cases [140]. The authors suggested defensive CSF puncture in case of pain (that was the only symptom reported), assuming as a cause a CFS focal temporary block.

Rodriguez et al. diagnosed isolated Syr in 98 children (37 with scoliosis); during the mean follow-up period of

20.5 months (1–143 months), only six out of 78 children (7.7%) showed clinical deterioration and three out of 38 (7.9%) larger syrinx (Table 8) [141].

Commentary

No eligible papers were found on syrinx secondary to spinal tumors, arachnoidal cysts, or spinal vascular malformations.

Two included papers pertain to Syr due to spinal dysraphism and they indicate the need of detethering surgery [138, 139]. The syrinx due to tethered cord has a typical low location next to the site of tethering, defined terminal Syr, and displays a progressive caudo-cranial extension [142]. Hence, the indication to extend the MRI study to the whole cord in Syr without CM1. The Erkan and coworkers' study suggests better results if fenestration of terminal syrinx is added; the study quality is low/unclear: randomization was "simple" leading to selection and allocation bias, no blinding assessment was done, the follow-up was short, and conclusions were based on a limited sample. So the suggestion to manipulate the conus, opening the syrinx, has a too low level of evidence to be a strong recommendation [138].

Despite its frequency, we found no eligible papers about syrinx secondary to spinal tumors: there were just case reports or case series with mixed ages. The indication of these papers is to perform always a contrast-enhanced MRI in Syr without CM1, and, if a tumor is present, its removal is usually enough to obtain syrinx shrinkage [143].

Neither for vascular malformations nor cysts, we found any eligible paper; the suggestion offered by case reports is to address surgery to the malformation [144] or to the cyst [145, 146] to obtain syrinx shrinkage.

Isolated Syr is quite rare. Little data are reported about its evolution, but the natural course seems favorable even without surgical treatment, with no correlation between clinical symptoms and MRI findings [137, 140, 141].

Table 8 Characteristics of the included studies for PICO 7

Study	Participants	Age *Mean (range)*	Design	Intervention	Comparator	Enrollment period	Follow-up *Mean (range)*	Outcome measures
Erkam et al. (2000)	30 children with terminal syringomyelia and tethered cord syndrome	6.2 years (1–16)	RCT, single center	16 standard untethering	14 untethering plus syrinx fenestration	03/1992–02/1998	12 months	Clinical MRI
Magge et al. (2011)	48 children with idiopathic syrinx (≥ 1 mm)	9.7 years (0.2–19.3)	Retrospective cohort, single center	NA	NA	10/2006–03/2009	23.8 months (2–64)	Clinical MRI
Lee et al. (2012)	33 children with syringomyelia (≥ 1 mm) and tethered cord (81% lipoma, 18% thickened filum)	6 months (1–192)	Retrospective cohort, single center	Untethering	NA	01/2003–12/2008	36 months (NR)	Clinical MRI Ultrasonography
Joseph et al. (2013)	39 children with isolated syringomyelia (≥ 1 mm)	10.6 years (3–16)	Retrospective cohort, single center	NA	NA	02/2007–08/2011	15.6 months (4–84)	Clinical MRI
Rodriguez et al. (2015)	61 children with isolated syrinx (≥ 0.5 mm) without scoliosis 37 children with isolated syrinx with scoliosis	11.9 years (0.1–18.4)	Retrospective cohort, single center	NA	NA	2002–2012	20.5 months (1–143) Clinical follow-up	Clinical MRI

[§]Info available for the entire cohort, not for the 6 with syrinx necessitating surgery

RCT, randomized controlled trial; *MRI*, magnetic resonance imaging; *SCI*, spinal cord injury; *NA*, not applicable; *NR*, not reported

The work by Vogel and coworkers focused on post-traumatic Syr (PTS) due to spinal cord injuries (SCI) during childhood; the authors collected a large series of 216 pediatric SCI cases with a long-term follow-up. They concluded that PTS with delayed deterioration is quite rare (3%) after pediatric SCI [147].

The role of Syr in patients with scoliosis remains an open problem: is it the cause or the consequence? The data seems to indicate that Syr is the cause of scoliosis. A scoliosis rate between 30 and 70% is reported in patients with CM1 and Syr and recently, through the analysis of a series of 825 patients with CM1 and Syr, 260 of whom with scoliosis, an association between the size of Syr and scoliosis, but not between the degree of tonsillar ectopia and scoliosis, has been demonstrated [148]. However, it is also possible that scoliosis can cause Syr since idiopathic syringes are common in scoliosis [148].

Rodriguez et al. found no statistical difference comparing radiological and clinical course in isolated Syr with and without scoliosis [141]. Furdock et al. reported the presence of Syr in 48 out of 267 (18%) spinal MRI of 305 pediatric scoliosis [149].

Taking into account scoliosis due to Syr, Yeom et al. reported a cut-off at the age of 10 years and Brockmayer et al. a curve angle inferior to 40° to obtain the regression of scoliosis without fixation when Syr is correctly treated [150, 151]. Samdani et al. underlined the impact of Syr size on the outcome after surgical correction of scoliosis and risk of worsening along fixation due to intraoperative neurophysiological monitoring failure [152].

Sha et al. reported comparable results in idiopathic and Syr-related scoliosis by thoracic fixation in 28 children and Qin and coworkers proposed selective thoracic fusion as the best choice treatment for Syr-associated scoliosis in a case–control study [153, 154]; unfortunately in both studies, details about causes of Syr and its previous neurosurgical treatments were lacking.

Conclusions

In conclusion, CM1 with or without Syr and Syr without CM1 still represent clinical challenges. As more is discovered about the natural history of untreated children and the long-term outcome of the treated ones, the management of these conditions continues to evolve.

The available evidence about the management of children with CM1 and Syr can be summarized as follows:

1) Asymptomatic or mildly symptomatic CM1 children without Syr generally have a benign prognosis (at least over the short intervals reported in the literature), as they may improve or remain symptomatically stable with conservative management. However, they need to maintain long-term clinical and radiological follow-up because the risk of worsening is low but not nil; about 5% of them require surgical treatment during follow-up.

2) Symptomatic CM1 children, which represent a low rate of CM1 children at the time of diagnosis, and CM1 patients with Syr have indications for surgery. Posterior fossa decompression surgery involves both clinical and radiological improvement with the ascent of the cerebellar tonsils and stabilization or improvement of Syr in a high percentage of children. The complication rate is very low (0 to 2.4%); from 3 to 20% of treated children require a reintervention for persistent Syr in most cases, rarely because of unchanged symptoms.

It is not clear, however, when to decide for surgery because little is known about the natural history of symptomatic CM1 children without Syr, there are no defined and generally accepted strict criteria for selecting patients for surgery, there are no validated methodologies for predicting which children will show worsening of symptoms and for deciding whether to intervene or not and the decision for suboccipital decompression can be subjective.

3) PFDD is associated with statistically significant longer operation time and hospitalization, and higher complication rates than PFDO. The comparison between PFDO and PFDD does not allow any further conclusion as the reported series were limited by small sample size, lack of clear and more homogeneous characterization of patients, and adequate criteria for outcomes selection and evaluation and a long-term follow-up. Large collaborative studies with proper design are necessary.

4) Taking into account the limitations related to missing high-level evidence studies, the present analysis allows to answer to PICO 4 as follows: (a) CM1-associated hydrocephalus can be successfully treated by ETV and should be addressed first to treat the raised ICP and select children needing PF decompression; (b) the management of craniosynostosis-related CM1 should contemplate first the treatment of the synostosis, if this is early detected. In case of late diagnosis, the best therapeutic option can be found by assessing the possible raised ICP; (c) in case of CM1 associated with an obvious tethered cord, the management of the two conditions should be separated, starting with the most symptomatic of them (tethered cord is treated by spinal cord detethering, CM1 by posterior fossa decompression). On the other hand, there is not enough evidence yet to support the (extradural) section of the filum terminale to treat symptomatic CM1 children with "occult tethered cord."

5) CVJ anomalies are quite commonly associated to CM1. In case of complex CM1, the therapeutic options should be pondered according to the degree of ventral compression and the presence of instability, ranging from pos-

terior decompression alone to posterior decompression and occipito-cervical fixation to ventral decompression and occipito-cervical fixation (with posterior decompression). Therefore, posterior decompression maintains its value in subjects without instability. There is not enough evidence yet to support the use of (occipito-) cervical fixation without obvious instability to manage pediatric CM1. The need to look for possible instability in children without evident CVJ anomalies is debated.
6) Complications and failures of CM1 surgery still represent a problem, but the criteria for follow-up and reintervention and the type of redo surgery are lacking.
7) Syr without CM1 is a rare occurrence. The few available data indicate to address first, if identified, the possible cause (dysraphism, tumor, vascular malformation, arachnoiditis); isolated Syr without CM1 seems to have an indolent course.

In summary, despite decades of experience, the management of children with CM1 and Syr remains unclear and controversial due to the lack of large, prospective, high-quality clinical trials on well-defined patient populations, and sufficient follow-up. The first prospective randomized clinical trial, organized by the Park-Reeve Syringomyelia Research Consortium, comparing PFDO and PFDD in a large group of homogeneous patients (NCT02669836), represents the first step to achieve an evidence-based consensus for surgical decision-making [155].

The Italian "Chiari-Syringomyelia Consortium," made up of doctors (neurologists, neurosurgeons, neuroradiologists, physiatrists, neurourologists, psychologists, speech therapists, of pain), public health experts for rare diseases, and representatives of patient associations, proposed diagnostic, surgical, and rehabilitative recommendations on CM1 and Syr derived from the results of the Consortium meetings and of the "First Chiari Consensus Conference" held in Milan in 2009 [156].

The present review served at the 2019 "Chiari and Syringomyelia Consensus Conference" which was held in Milan with the aim of bringing together experts to share collaborative initiatives focusing on the adoption of shared inclusion criteria and outcome measures, as well as rigorous prospective designs, for the development of evidence-based strategies [8, 9].

Appendix 1

Table 9 The PICO-questions

Clinical question 1	**For asymptomatic CM1 children, which are the effects of neurosurgery vs. conservative management on outcome?**
Population	Asymptomatic CM1 Children (0-18 years) with/without Syringomyelia
Intervention	Surgery
Comparator	No surgery, clinical and radiological follow-up
Outcomes	1. Symptoms/signs burden 2. Radiological outcomes: tonsillar ectopia, syrinx, hydrocephalus, CSF flow 3. Quality Of Life (QOL) 4. Surgical complications
Clinical question 2	**For symptomatic CM1 children, which are the effects of neurosurgery vs. conservative management on outcome?**
Population	Symptomatic CM1 children (0-18 years) with/without syringomyelia
Intervention	Surgery
Comparator	No surgery, clinical and radiological follow-up
Outcomes	1. Symptoms/signs burden 2. Radiological outcomes (tonsillar ectopia, syrinx, hydrocephalus, CSF flow) 3. QOL 4. Surgical complications
Clinical question 3	**For children with CM1 selected for surgery, without associated malformations, is bone cranio-vertebral decompression the most effective intervention?**
Population	CM1 children (0-18 years)with/without syringomyelia
Intervention	Bone cranio-vertebral decompression
Comparator	Plus duraplasty with/without tonsillar resection
Outcomes	1. Symptoms/signs burden 2. Radiological outcomes (tonsillar ectopia, syrinx, hydrocephalus, CSF flow) 3. QOL 4. Surgical complications

Table 9 (continued)

Clinical question 4	**For children with CM1 and associated malformations (hydrocephalus or craniosynostosis or tethered cord), is cranio-vertebral decompression more effective than other surgical approaches?**
Population	Symptomatic CM1 children (0-18 years) with/without syringomyelia and hydrocephalus or craniosynostosis or tethered cord
Intervention	Cranio-vertebral decompression
Comparator	Other surgical approaches (shunt or endoscopy, cranioplasty of cranial vault distraction, detethering)
Outcomes	1. Symptoms/signs burden 2. Radiological outcomes (tonsillar ectopia, syrinx, hydrocephalus, CSF flow) 3. QOL 4. Surgical complications
Clinical question 5	**For CM1 children with Cranio-vertebral Junction Malformation, is cranio-vertebral decompression more effective than other surgical approaches?**
Population	Children (0-18 years) with CM1 and CVJM with/without syringomyelia
Intervention	Cranio-vertebral decompression
Comparator	Other surgical approaches (transoral approaches, posterior fixations, etc.)
Outcomes	1. Symptoms/signs burden 2. Radiological outcomes (tonsillar ectopia, syrinx, hydrocephalus, CSF flow) 3. QOL 4. Surgical complications
Clinical question 6	**For children with failed CM1 surgery, is early redo surgery (≤ 12 months) more effective than late redo (>12 months) or no surgery?**
Population	Already operatedCM1 Children (0-18 years) with persistence of symptoms and/or syringomyelia at 12 months
Intervention	Redo surgery within 12 months
Comparator	Redo surgery > 12 months or clinical follow-up
Outcomes	1. Symptoms/signs burden 2. Radiological outcomes (tonsillar ectopia, syrinx, hydrocephalus, CSF flow) 3. QOL 4. Surgical complications
Clinical question 7	**For children with Syringomyelia without CM1, which is the most effective clinical, radiological and surgical planning?**
Population	Children (0-18 years) with Syringomyelia (without CM1). Syrinx secondary to spinal tumor, vascular malformation, tethering, arachnoiditis or isolated
Intervention	Clinical and radiological follow-up
Comparator	Etiological surgery and/or shunting
Outcomes	1. Symptoms/signs burden 2. Radiological outcome (syrinx evolution) 3. QOL 4. Surgical complications

Appendix 2: Search strategies for Medline (PubMed)

((("Arnold-Chiari Malformation"[Mesh] OR "Chiari malformation"[Title/Abstract] OR "arnold-chiari"[Title/Abstract] OR "arnold-chiari malformation"[Title/Abstract] OR "chiari type 1.5 malformation"[Title/Abstract] OR "Chiari malformation type 1"[Title/Abstract] OR "Chiari malformation type I"[Title/Abstract] OR "Chiari I"[Title/Abstract] OR "Chiari 1"[Title/Abstract] OR "Chiari type 1"[Title/Abstract] OR "Chiari type I"[Title/Abstract]))) OR (("Chiari syndrome"[Title/Abstract]) NOT Budd-Chiari Syndrome))) NOT (((((("Chiari Malformation Type 2"[Title/Abstract]) OR "Chiari Malformation Type II"[Title/Abstract]) OR "Type II Arnold-Chiari Malformation"[Title/Abstract]) OR "Chiari type II"[Title/Abstract]) OR "Chiari type 2"[Title/Abstract])))

NOT ((animals[MeSH Terms]) OR (animals[MeSH Terms] AND humans[MeSH Terms]))

Filters: Child: birth-18 years

Filters: Publication date from 1999/01/01 to 2019/05/22

"Syringomyelia"[Mesh] OR (Syringomyelia[Title/Abstract] OR Syringomyelias[Title/Abstract] OR Syringomyelus[Title/Abstract] OR syrinx[Title/Abstract] OR Syringobulbia[Title/Abstract] OR Myelosyringosis[Title/Abstract] OR "Morvan Disease"[Title/Abstract] OR "Morvan Diseases"[Title/Abstract] OR "Morvan's Disease"[Title/Abstract] OR "Morvan's Diseases"[Title/Abstract] OR "Morvans Disease"[Title/Abstract] OR Hydrosyringomyelia[Title/Abstract] OR Hydromyelia[Title/Abstract])

NOT ((animals[MeSH Terms]) OR (animals[MeSH Terms] AND humans[MeSH Terms]))
Filters: Child: birth-18 years
Filters: Publication date from 1999/01/01 to 2019/05/22

Appendix 3

Table 10 Risk of bias for the included trials [12]

Study	Sequence generation *(selection bias)*	Allocation concealment *(selection bias)*	Blinding of participants and personnel *(performance bias)*	Blinding of outcome assessment *(detection bias)*	Incomplete outcome data addressed *(attrition bias)*	Selective reporting *(non-reporting bias)*	Other sources of bias
PICO 3							
Jiang et al. 2018	low risk	low risk	high risk	unclear	unclear	unclear	low risk (but underpowered)
PICO 7							
Erkan et al. 2000	unclear	unclear	unclear	unclear	low risk	unclear	unclear

Table 11 Risk of bias for the cohort studies [11]

Study	1. Focused question	2. Cohort recruitment acceptable *(selection bias)*	3. Subject classificationacceptable *(classification bias)*	4. Outcomes acceptable *(detection bias)*	Confounders 5a. identified 5b. adjusted for	Follow-up 6a. complete 6b. long enough *(selection bias)*
PICOs 1, 2						
Anderson et al. 2003	No	Can't tell	Yes	Yes	No/No	Yes/ Can't tell
Tubbs et al. 2003	No	Can't tell	Yes	Can't tell	No/No	Can't tell/ Can't tell
Novegno et al. 2008	Yes	No	Can't tell	Can't tell	No/No	Yes/No
Aitken et al.2009	Yes	Yes	Can't tell	Can't tell	No/No	Yes/No
Benglish et al. 2011	Yes	No	Yes	Can't tell	No/No	Yes/No
Massimi et al. 2011	Yes	No	Can't tell	Can't tell	No/No	Yes/No
Strahle et al. 2011	Yes	No	Can't tell	Can't tell	No/No	No/No
Killeen et al. 2015	Yes	No	Can't tell	Can't tell	No/No	No/No
Whitson et al. 2015	Yes	Yes	Yes	Can't tell	Yes/No	Can't tell/ Can't tell
Pomeraniec et al. 2016	Yes	No	Can't tell	Can't tell	No/No	No/No
Leon et al. 2019	Yes	Can't tell	Yes	Can't tell	Can't tell/Yes	No/No
Tubbs et al. 2011	Yes	Can't tell	Can't tell	Can't tell	No/No	Can't tell/ Can't tell
Knerlich-Lukoschus et al. 2019	Yes	Can't tell	Can't tell	Can't tell	No/No	Can't tell/ Can't tell
PICO 3						
Navarro et al. 2004	Yes	Can't tell	Can't tell	No	No/No	Can't tell/No
Yeh et al. 2006	Yes	Can't tell	No	Can't tell	No/No	Can't tell/No
Galarza et al. 2007	Yes	Can't tell	Can't tell	Can't tell	No/No	Can't tell/ Can't tell
McGirt et al. 2008	Yes	Yes	Yes	Yes	Yes/Yes	Can't tell/ Can't tell
Shamij et al. 2010 Venturyra et al. 2003 (§)	No	Can't tell	Can't tell	Yes	No/No	Can't tell/No
Litvack et al. 2013 Limonadi et al. 2004 (§§)	Yes	Yes	Can't tell	No	No/No	Can't tell/Yes
Chotai et al. 2014	No	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell/ Can't tell

Table 11 (continued)

Study	1. Focused question	2. Cohort recruitment acceptable *(selection bias)*	3. Subject classificationacceptable *(classification bias)*	4. Outcomes acceptable *(detection bias)*	Confounders 5a. identified 5b. adjusted for	Follow-up 6a. complete 6b. long enough *(selection bias)*
Lee A et al. 2014	Yes	Yes	Can't tell	Yes	No/No	Can't tell/No
Lee S et al. 2014	No	Can't tell/no	Yes	Yes	No/No	Can't tell/Yes
Narenthiran et al. 2015	Yes	Can't tell	Yes	Yes	No/No	Can't tell/No
Pomeraniec et al. 2015	Yes	Yes	Yes	Yes	No/No	Yes/Can't tell
Shweikeh et al. 2015	No	Yes	Yes	No	No/No	Can't tell/No
Gallo et al. 2017	Yes	Yes	Yes	Yes	No/No	Can't tell/Yes
Pisapia et al. 2017	Yes	Yes	Yes	Can't tell	No/No	Yes/No
Raza Knightn et al. 2017	Yes	Yes	Yes	Can't tell	No/No	Can't tell/NO
Grahovac et al. 2018 (§§§)	Yes	Can't tell	Yes	Yes	No/No	Can't tell/Yes
Entezami et al. 2019	No	Can't tell	Can't tell	No	No/No	Can't tell/NO
Gernsback-Tomita et al. 2019 (§§§)	Yes	Can't tell	No	Yes	No/No	Can't tell/ Can't tell
Walker-Palmer et al. 2019	Yes	Can't tell	Yes	Yes	No/No	Can't tell/ Can't tell
(§) Shamij et al. 2010 is an update of Venturyra et al. 2003;(§§) Litvack et al. 2013 is the update of Limonadi et al. 2004;(§§§)Probable overlap between the two populations						
PICO 4						
Tubbs et al. 2003	No	Can't tell	Yes	Can't tell	No/No	Can't tell/ Can't tell
Tubbs et al. 2011	No	Can't tell	Yes	Can't tell	No/No	Can't tell/ Can't tell
Strahle et al. 2011bis	Yes	Yes	Yes	Yes	No/No	Can't tell/ Can't tell
Karppinen et al. 2012	No	Yes	Yes	Yes	No/No	Yes/No
Addo et al. 2013	Yes	Yes	Yes	Yes	No/No	Can't tell/ Can't tell
Scott et al. 2013	Yes	Yes	Yes	Yes	No/No	Can't tell/Yes
Glenn et al. 2015	Yes	Yes	Yes	Yes	No/No	Can't tell/ Can't tell
Balestrino et al. 2019	No	Can't tell	Yes	Yes	No/No	Yes/ Can't tell
PICO 5						
Grabb et al. 1999	No	Can't tell	Yes	Yes	No/No	Can't tell/ Can't tell
Kim et al. 2004	Yes	Can't tell	No	Yes	No/No	Yes/No
Bollo et al. 2012	Yes	No	Can't tell	Can't tell	Yes/Yes	Can't tell/ Can't tell
Goel et al. 2018	Yes	Can't tell	Can't tell	Yes	No/No	Yes/No
PICO 6						
Tubbs et al. 2004	Yes	Can't tell	Yes	Yes	No/No	Can't tell/Can't tell
Kennedy et al. 2015	Yes	Yes	Yes	Yes	Yes/Yes	Yes/ Can't tell
PICO 7						
Vogel et al. 2002	No	Can't tell	Can't tell	Can't tell	No/No	Can't tell/Can't tell
Magge et al. 2011	Yes	Yes	Yes	Yes	No/No	Yes/Can't tell
Lee et al. 2012	Yes	Can't tell	Yes	Can't tell	No/No	Can't tell/Can't tell
Joseph et al. 2013	Yes	Yes	Yes	Yes	No/No	No/Can't tell
Rodriguez et al.2015	Yes	Can't tell	No	Yes	No/No	No/Can't tell

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Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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