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ORIGINAL ARTICLES AND REVIEWS

Syringomyelia and Chiari Syndrome Registry: advances in epidemiology, clinical phenotypes and natural history based on a North Western Italy cohort

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Abstract

Background. Syringomyelia and Chiari Syndrome are classified as rare diseases, but current known occurrence in Europe is missing. The increased ability to diagnose these pathologies by magnetic resonance imaging and its widespread availability has led to an increase of reported cases, often asymptomatic, with the need to standardize definitions, diagnostic criteria and treatments.

Aims. We present shared Interregional Recommendations developed with the primary aim to estimate Syringomyelia and Chiari Syndrome prevalence and incidence in North Western Italy, with special reference to symptomatic forms.

Methods. An agreement for the standardization of definitions, classifications, diagnostic criteria and surgical Recommendations was reached by the multidisciplinary Interregional Piemonte and Valle d'Aosta Chiari-Syringomyelia Consortium (Delphi method); next, in 2011 a census for Syringomyelia and Chiari Malformation was performed through the Interregional Piemonte and Valle d'Aosta Rare Disease Registry, integrated by a dedicated form in order to estimate prevalence and incidence.

Results. 436 patients, 292 females, met shared interregional diagnostic criteria. Syringomyelia prevalence was estimated in 4.84:100 000; Chiari Malformation prevalence was 7.74:100 000; incidence was 0.82:100 000 and 3.08:100 000 respectively. Demographics, neuroradiological parameters and aetiology were reported (in symptomatic and asymptomatic forms). Finally, symptoms and signs, familiar and natural history were analyzed.

Conclusions. First Italian epidemiological data (prevalence, incidence) on Chiari and syringomyelia was collected, according to shared diagnostic Recommendations. Future perspectives include the adoption of these Recommendations at national level to standardize the access to diagnosis and care process and promote multicenter clinical trials.

Key words
- epidemiology
- rare disease
- Syringomyelia
- Chiari Malformation
- recommendations

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INTRODUCTION

Syringomyelia (Syr) is morphologically defined at magnetic resonance imaging (MRI) as the presence of single or multiple fluid-filled cavity (syrinx) within the parenchyma of the spinal cord and/or the bulb (Syringobulbia) and classified as a rare disease (ORPHA3280). About 50% of Syr patients have severe neurological damage, chronic-progressive disability with complete loss of independence. Prognostically speaking, even more unfavourable is the presence of Syringobulbia (swallowing and breathing bulbar centers involved). Before 1968, neurologists diagnosed Syr only by typical neurological symptoms. Since the introduction of CT myelography and MRI techniques for spinal cord imaging, the diagnosis has become easier, and many cases have been reported. In studies conducted before the advent of modern neuroimaging, prevalence ranged from 3.3 to 8.5/100 000 [1-3]; after the advent of MRI estimated prevalence ranged from 1.9 to 8.4/100 000 [4, 5].

Chiari Malformation (CM) includes a heterogeneous group of abnormalities characterized by the caudal cerebellum ptosis through the foramen magnum; clinical manifestations define the Arnold-Chiari or Chiari Syndrome (CS). The malformation can cause a wide variety of neurological symptoms, often vague or nonspecific, such as headaches, ocular disturbances, otoneurologic disturbances, lower cranial nerve signs, cerebellar ataxia, or spasticity [6]. Onset of symptoms is usually in the third decade of life. However, many individuals with CM remain asymptomatic even later in life. A US study estimated 400 000 patients affected by Chiari type 1 Malformation (CMI), the most common CM type. The epidemiology of CMI malformation has been scarcely investigated. The true population prevalence of CMI is unknown and there are no studies on CMI incidence. A retrospective analysis of more than 22 000 neuroimaging diagnoses [7] provided indirect data of CMI prevalence, estimable in 1:1280 (0.77%). When CM is defined by cerebellar tonsil position 5 mm or more below the foramen magnum, imaging prevalence studies estimate CM prevalence at between 0.24 and 3.6% of the population [8]; the discrepancy between these estimates is a result of the different age groups analysed, substantially higher in children and young adults compared with older adults. In Italy and in the European Community the CMI is classified as a rare disease (ORPHA268882), but current known occurrence data in Europe is missing.

The increased ability to diagnose CM and Syr by MRI and its widespread availability has led to an increase of reported cases, often asymptomatic or minimally symptomatic, with the need to standardize definitions, diagnostic criteria and treatments.

In 2001 DM 279/2001, National Law [9] set up the Italian National Network for rare diseases, to deal with the prevention, surveillance, diagnosis and treatment of rare diseases (RD), including Arnold-Chiari or Chiari Syndrome; the same law activated the RD National Registry located at the Istituto Superiore di Sanità, which is expected to receive epidemiological data from Regional Registries. A Regional Decree (2/3/2004, n. 22-11870) established the Piemonte Regional Network for the prevention, screening, diagnosis and therapy of RD. Moreover, it obliges the Hospital Units to report RD in the Regional Registry [10], with epidemiological and legislative purposes (i.e. to regulate the access on exemption path for RD). In 2005 because of the low prevalence estimates, the potential clinical severity in chronically debilitating nature and the resulting significant expense for its treatment, Syr was inserted as RD involving the nervous system in Piemonte and Valle d'Aosta [11]. Now, with the adoption of the new National law on Essential Assistance Levels [12], Syr is recognized also as RD in all Italian regions, but previously this was recognized as RD only in Piemonte, Valle d'Aosta, Toscana and Marche; for this reason Italian epidemiological data on Syr was not available in the RD National Registry.

Syr and CM are classified as rare diseases on Orphanet, the International reference portal for RD and orphan drugs, but current prevalence data is missing.

Guidelines on diagnostic criteria and case definition are missing, and consequently estimation of the prevalence in Piemonte and Valle d'Aosta for symptomatic and asymptomatic forms are missing.

In 2008 a consortium dedicated to the study of Syr and CM began its activity in the Piemonte and Valle D'Aosta regions, as part of the Rare Diseases Network of the Italian National Health Service, with the aims to standardize/share definitions, classifications, care and diagnostic approaches.

The consortium, named the Interregional Chiari-Syringomyelia Consortium (CSC), was composed by clinicians (neurologists, neurosurgeons, neuroradiologists, physiatrists, neuro-urologists, psychologists, speech pathologists, spinal surgeons, pain specialists), experts of public health for RD, and patient association representatives [13]. In 2010 the CSC Recommendations were proposed: some of these indications derived from the outcomes of the CSC meetings, others were from the First International Chiari Consensus Conference, held in Milan in 2009 [14].

Diagnostic, Surgical and Rehabilitative Recommendations were approved by the members of Technical-Specialized Task-force supporting the Regional Center of Coordination for RD and by the following scientific societies: Italian Society of Neurology, Piemonte and Valle d'Aosta section; Italian Society of Neurologists, Neurosurgeons, Neuroradiologists, Piemonte-Valle d'Aosta-Liguria section; Italian Society of Physical Medicine and Rehabilitation, Piemonte section [15]. The document was published as technical-scientific integration of the Regional Legislation (DGR n. 95-13748, 29 March 2010), specifying the Institution of the first Center of Expertise for Chiari and Syringomyelia in Torino [16, 17].

In this study, based on the Interregional Recommendations, we present the first estimation of prevalence and incidence of Syr and CM in North Western Italy (Piemonte and Valle d'Aosta), with special reference to symptomatic forms (Symptomatic Syringomyelia: SS; Chiari Syndrome: CS).

MATERIAL AND METHODS

Interregional recommendations

In order to estimate the epidemiological indices (prevalence and incidence), the diagnostic criteria used

for case definition was based on the Interregional Diagnostic, Surgical and Rehabilitative Recommendations. The Recommendations were developed following several steps: a) collecting all available evidence on clinical studies related to Syr and CM. The following databases were queried for literature review on Syr and CM: Medline (PubMed interface, www.pubmed.gov), Cochrane Library (Health Library of Piedmont, www.bvspiemonte.it), National Guidelines Clearinghouse (www.guideline.gov). The literature searching strategy was conducted by combining: the Medical Subject Heading (MeSH): "Arnold-Chiari Malformation" or "Syringomyelia" or "Arnold-Chiari Malformation" AND "Syringomyelia"; Publication type (PT): "Systematic Reviews", "Practice Guideline", "Meta-Analysis", "Randomized Controlled Trial"; b) assessing studies for relevance. All studies were selected and critically evaluated. Results with low evidence level were restricted for date (last 10 years) and language (English, French, German, Spanish, Italian); these were also selected and critically evaluated; c) categorising the evidence. Each expert member expressed an evaluation of the articles, giving a score between 0 (strongly disagree) and 10 (strongly agree), according to the Delphi method [18]. If there was an agreement, the document was revisited in textual form and submitted to the working group for the final approval and subsequent drafting of the ultimate document; for evaluation lower or equal to 7 it was necessary to propose an alternative text version and relative notes. If no agreement was reached, the document came back to the recommendation authors with comments for necessary changes and resubmitted to the experts involved. When an agreement was reached, the document in the preliminary form was prepared and submitted to the judgment of the entire experts group for final consensus. A description of the sections of the Recommendations including classifications, radiological and clinical definitions, surgical and conservative indications are reported in *Table 1* and *Table 2*.

Census study

According to these Recommendations, in 2011 a Syr and Chiari census study was performed through the Interregional Piemonte and Valle d'Aosta Registry of RD, integrated by a dedicated Case Report Form, reported in *Figure 1*; the CSC form was developed by the Chiari-Syringomyelia Consortium and filled out by every specialist (neurologist or neurosurgeon) involved in the diagnosis.

We integrate the data extracted from the RD Registry (minimal data set) with the CSC form in order to estimate Syr and Chiari prevalence and incidence; moreover, the CSC form enriched the information providing further socio-demographics and clinical data. The study was approved by the Local Ethic Committee ("Prospective collaborative epidemiologic, clinic and genetic study in CM with and without Syr, hereditary connective tissue disorders and tethered cord", Protocol n. 7837, 1/2/2010, Città della Salute e della Scienza di Torino Hospital, Turin). All partecipants gave signed informed consent at the time of inclusion in the census study.

Statistical analysis

Up to 31 December 2011, the Syr and Chiari age standardized prevalence and the incidence rate in 2011 with 95% confidence intervals (95% CI) in Piemonte and Valle d'Aosta Regions was estimated. The prevalence (number of alive diagnoses up to 2011 year) and the incidence (number of new reported cases in 2011 year) were estimated using both the Interregional Piemonte and Valle d'Aosta Rare Disease Registry and the CSC census data for symptomatic forms. The CSC census data was also used to analyse asymptomatic forms. The standardization was performed by a direct method using the Italian census population at 1st January 2011 year (respectively 4 457 335 inhabitants in Piemonte and 128 230 in Valle d'Aosta, 4 585 565 total population), according to ISTAT census data (2012) [18, 19]. Confidence intervals were calculated assuming a Poisson distribution.

Basic statistics in terms of frequencies (absolute and percentage values) were calculated for: socio-demographic data, age at diagnosis, age at survey, diagnostic delay, MRI parameters (morphology/level), diagnoses, associated conditions, neurological symptoms/signs, types of surgery.

All statistical analyses were performed using the Stata statistical software (StataCorp. Statistical Software: Release 7.0. College Station, TX: Stata Corporation. 2001).

RESULTS

Census results

Using CSC form, 436 patients (292 females and 144 males) met shared diagnostic criteria for Syr and/or CM (*Table 3*). Demographics, MRI parameters (morphology/level), diagnoses, associated conditions, estimated prevalence and incidence data were reported respectively in 347 CM patients and in 217 patients affected by Syr. Percentage of symptomatic Chiari (CS) and symptomatic Syr (SS) are represented in *Figure 2*. In 2011 the estimated Syr prevalence is 4.84:100 000 and incidence is 0.82:100 000; the estimated CM prevalence is 7.74:100 000, incidence 3.08:100 000 (*Table 4* and *Table 5*).

Description of clinical manifestations

Major neurological symptoms in CS and in SS were respectively: headache (48% and 28%), cervical pain (30% and 24%), loss of balance (30% and 18%). Major neurological signs in CS and in SS respectively were: sensory disorders (48% and 70%), motor disorders (32% and 60%), cranial nerves (41% and 40%), autonomic bladder disorders (14% and 19%). Neuropathic pain, defined on the basis of a DN4 questionnaire score higher or equal than 4 [30], was 19% in CS and 32% in SS. Familiar history was positive in 5% in CS and in 2% in SS (familiar forms); pregnancy was carried out by vaginal delivery in 67% and 55% respectively in CS and SS, while by caesarean delivery (general anaesthesia) in 23% and 35%. Scoliosis was reported in 29% of all CM and 32% of all Syr; 43 patients (25%) presented with scoliosis, CM1 and Syr.

In our study females are prevalent in all groups (*Table*

Table 1
Diagnostic Recommendations for Chiari 1 Malformation and Syringomyelia (elaborated by the Interregional Chiari and Syringomyelia Consortium)

Chiari Malformation (CM) classification
CM is a congenital anomaly of the cerebellum associated or not with neural tube defects
1. CM I: paraxial mesoderm disorder, with abnormalities of the posterior cranial fossa (mostly small) and the consequent descent of the cerebellar tonsils
   CMI-A: with Syr in MRI
   CMI-B: without Syr in MRI
2. CM II: associated with myelomeningocele (prevalent in childhood), hydrocephalus, and, less frequently, hydrosyringomyelia Other types of intracranial defects (hypoplastic tentorium cerebelli, cranial lacunae, anomalies of the Sylvius aqueduct) may exist
3. CM III: intracranial defects associated with Chiari II Malformation (very rare and severe form)
4. CM IV: cerebellar aplasia or hypoplasia, associated with aplasia of the tentorium cerebelli [21]

Chiari Malformation: "subtypes" classification
1. Classical CMI + craniosynostosis + osteopetrosis
2. CMII + Tethered Cord Syndrome (TCS)
3. CMI + inherited disorders of connective tissue-HDCT (i.e. Ehlers-Danlos syndrome)
4. Hypertension intracranial + hydrocephalus + space occupying process
5. Hypotension intraspinal CSF + lumbo-peritoneal shunting [22]

Chiari Malformation (neuroradiological) definition
According to IHS diagnostic criteria (the second updated edition of "International Classification of Headache Disorders", code 7.7), cerebellar tonsillar herniation is defined by one of the following on craniocervical MRI:
- ≥ 5 mm caudal descent of the cerebellar tonsils
- ≥ 3 mm caudal descent of the cerebellar tonsils plus at least one of the following indicators of crowding of the subarachnoid space in the area of the craniocervical junction:
- compression of the CSF spaces posterior and lateral to the cerebellum
- reduced height of the supraocciput
- increased slope of the tentorium
- kinking of the medulla oblongata [23]

Chiari Syndrome definition
CS is the clinical manifestation (symptoms and signs) of CM (radiologically defined), or "symptomatic Chiari".
Clinical diagnostic criteria (symptoms and neurological signs) are:
1. Headache, according to IHS diagnostic criteria characterised by at least one of the following criteria:
   - precipitated by cough and/or Valsalva manoeuvre
   - occipital and/or sub-occipital headache
   - associated with symptoms and/or signs of brainstem, cerebellar and/or cervical cord dysfunction
2. Otoneurogical symptoms and/or signs (eg, dizziness, disequilibrium, sensations of alteration in ear pressure, hypacusia or hyperacusia, down-beat nystagmus, oscillopsia)
3. Transient visual symptoms (spark photopsias, visual blurring, diplopia or transient visual field deficits)
4. Demonstration of clinical signs relevant to cervical cord, brainstem or lower cranial nerves or of ataxia or dysmetria

Notes: for the diagnosis of Chiari Syndrome, in addition to the typical headache (criterion 1), neurological symptoms/signs (at least two of criteria 2-4), evidence of posterior fossa dysfunction, are mandatory [23]

Syringomyelia/Hydromyelia: classification and definition
1. Type I: with obstruction of the foramen magnum and dilation of the central spinal canal
A) Associated with CMI
B) Associated with other obstructive lesions of the foramen magnum
2. Type II: syringomyelia without obstruction of the foramen magnum, or idiopathic
3. Type III: syringomyelia with other diseases of the spinal cord
   A) Spinal cord tumours (usually intraspinal)
   B) Traumatic myelopathy
   C) Spinal arachnoiditis and pachymeningitis
   D) Myelomalacia due to compression of the spinal cord (tumour, spondylosis)
4. Type IV: pure hydromyelia, developmental widening of the central canal of the spinal cord, usually associated with hydrocephalus

Notes: 1) The diagnosis of Syringomyelia-Syringobulbia is attributable by neurologists or neurosurgeons in the presence of Syrinx/Syringobulbia at MRI in addition to spinal/bulbar signs related to the syrinx level. The clinical criteria are mandatory; 2) Hydromyelia is an intramedullary, centrally located, non-enhancing, slit-like cavitation, often localized short-segment and occurring in a non-enlarged or only slightly enlarged spinal cord ("idiopathic localized hydromyelia"); clinically, patients present without neurological deficits but unspecific pain syndromes; they lack electrophysiological alterations and progressive signs/symptoms specifically related to the spinal cord [24].

3), and in particular in the CM group (68%). A slight prevalence of employed compared to unemployed (student and retired person) is present in the Syr group. Maybe this is due to the small sample size in the pediatric subgroup in Syr (≤18 yrs, students = 11%) compared to CM (20%) with average age at diagnosis of 34 yrs (lower than 36 yrs of Syr group). This may have a significant social impact for the high prevalence of symptomatic forms in Syr (62%), potentially severely disabling, compared with a lower percentage (40%) of Chiari symptomatic forms (*Figure 2*, *Tables 4*, *5*). Percentage in the over 60 yrs subgroup (retired person) is similar in both groups (18% CM and 22% Syr, *Table 3*).

Among CM, isolated form (CMI-B) is more frequent

Table 2
Surgical Recommendations for Chiari 1 Malformation and Syringomyelia (elaborated by the Interregional Chiari and Syringomyelia Consortium)

CSC Surgical Recommendations
- CM I-B symptomatic (CS isolated): children and adults with headache (typical) + auditory/cerebellar/spinal/visual signs
- CM I-A (CM I + Syr): children and adults, symptomatic and asymptomatic, especially in the case of
  1) holocord syringomyelia
  2) evolutionary trend (clinical/MRI worsening),
  3) central syringe and Vaquero Index >0.5 [25] or eccentric syringe
  4) syringomyelia with syringobulbia (spinal/bulbar signes)

Notes:1 In children with CMI-A surgical indications are larger, even if asymptomatic (prognostic value of early surgery: disappearance/reduction of syringe), while in children with CM I-B (without syringe) surgical indications are not clear in asymptomatic forms ("wait and see", with clinical and neuroradiological follow-up); 2) Asymptomatic and isolated Syringomyelia: in children and in adults surgical indications are not clear; if symptomatic forms, no consensus for surgery; 3) Post-traumatic Syringomyelia: no indication for direct decompression at the time of initial injury; a strong recommendation for surgical intervention in the presence (setting) of motor neurologic deterioration; a weak recommendation against surgical intervention for patients developing sensory loss/pain syndrome or for asymptomatic but expanding syrinx [26, 27].

Neurosurgical strategies
- CM I-A (with syrinx) and CMI-B symptomatic
  First Line: C1 occipito-cervical decompression with dura opening and dural plastic
  In children with isolated CM, surgery can be limited to the bone decompression (delamination of the atlanto-occipital ligament), without duraplasty [28, 29]
- CM 1 and hydrocephalus
  First Line: third ventriculostomy by endoscopy
  Second Line: osteo-dural decompression of the posterior fossa
- Re-interventions
  For patients developing neurological deterioration and expanding syringe (failure of first/second Line surgery)

Notes:1) Surgical efficacy is inversely proportional to the number of treatments; 2) Section of the filum terminale (in presence of "occult" tethered cord) is not a procedure of choice in the treatment of Chiari Syndrome; spinal cord detethering in CMI is accepted only when a real tethered cord is associated.

(58%), while CMI-A type (CMI and Syr) is just 36%, according to literature data reporting association ranges 32-74%. CM type 2 (CMII) is reported in 1%; other associated conditions, such as retroflexed odontoid, hydrocephalus, Klippel-Feil, Tethered Cord Syndrome, are reported in 5% of the cohort. Syr type I (associated to CM1) is the prevalent clinical phenotype (59%), while isolated Syr is at 41% (18% pure hydromyelia, 14% secondary and 9% idiopathic). Males are more symptomatic than females in both symptomatic groups (47% in CS, 64% in SS), even if the estimations on gender and on measure of tonsillar herniation don't identify associated risk factors in CS patients.

Hydromyelia patients (Pure-Hydromyelia included) are less than a third of Syr and are mostly asymptomatic (82%); this result on MRI morphology confirms the trend of Hydromyelia in presenting a low risk of clinical evolution towards symptomatic forms (18%).

Negative prognostic factors in the Syr group, with higher percentage (> 50%) of symptomatic patients (SS), are identified (*Table 5*). MRI syrinx distribution: cranial level (syringobulbia 100%, cervical 61%) in focal/single cavity; MRI syrinx extension (multilevel or olocorde 81%); aetiology (Secondary 77% and Primary 74%). In CS (*Table 4*) positive prognostic factor (poor/any clinical evolution) at MRI morphology (as tonsillar herniation length ≥5 mm/3-4 mm/<3 mm) is a tonsillar descent <3 mm (100% in ACM), while a descent ≥5 mm is not a significant prognostic indicator to clinical evolution in CS.

Among different clinical phenotypes: CMII is the less frequent and the most severe form (100% CS); CMI-A and other associated condition forms are symptomatic in approximately 60% of cases; CMI-B (isolated Chiari) is mostly asymptomatic with just 25% of CS (*Table 4*).

A high percentage of SS patients has sensory and motor disturbances (respectively 70% and 60%); neuropathic pain is relevant in Syr (32%), much more frequent than in CS group (19%). Percentage of autonomic disturbances (bladder dysfunction) is similar in both groups (19% SS *vs* 14% CS). Familiar forms are reported, confirming a role for genetic factors in the disease pathogenesis.

DISCUSSION

This study reports diagnostic and surgical Recommendations for Chiari and Syr, according to the International Consensus Conference in Milan in 2009, including a panel of experts, developed by the Interregional Piemonte and Valle d'Aosta Chiari and Syringomyelia Consortium [13, 14, 15].

Based on these diagnostic Recommendations, the first Italian epidemiological study for CM and Syr was designed to estimate prevalence and incidence in symptomatic and asymptomatic forms.

Our census study involved patients diagnosed in Piemonte and Valle d'Aosta hospitals, with a total population of 4 484 469 inhabitants, with a 99% Caucasian ethnic group. The prevalence estimation for Syr was similar to that reported in a New Zealand study [4] relative to prevalence in Caucasians (5.4/100 000), but was higher than the results of a nationwide survey in Japan, where prevalence was estimated in 1.9/100 000 [5]. We reported, to our knowledge, the first incidence estimates for Syr and Chiari in literature at international level.

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CHIARI-SYRINGOMYELIA CENSUS FORM

Center Name:	Country:	Date: / /
Patient:	Birthplace:	Birth date: / /
Residence:	Gender: ☐F ☐ M	Occupational status: ☐ Employed ☐Unemployed*
Partecipant Race: ☐White	☐ Black ☐ Hispanic ☐ Asian	☐ Other: _____

Medical history and family
MC/Syr familiarity: ☐YES ☐ NO (if yes, affected relative: _____)
Scoliosis: ☐YES ☐ NO
Pregnancy: ☐YES ☐NO (if yes: ☐physiological delivery ☐general anaesthesia)
Surgery: ☐MC ☐ Syr ☐ MC+Syr Number of surgery: ___
- Date : / /
- PFD**: ☐YES ☐ NO
- (if yes: ☐bony ☐osteo-dural ☐ osteo-dural+ duraplasty ☐osteo-dural+ tonsillar coagulation)
- Other Type: _____

Pathological MRI: ☐Brain ☐Spinal cord ☐Brain+spinal cord

Signs and symptoms:
☐Headache ☐Loss of balance ☐Cervical pain ☐ Dysphagia ☐ Nystagmus ☐ Neuropathic pain
☐Hyposthenia UL *** ☐Hyposthenia LL**** ☐ Upper MTN signs***** ☐ Lower MTN signs*****
☐Paraparesis ☐ Tetraparesis ☐Paraplegia ☐ Tetraplegia ☐ Spasticity ☐Hypoaesthesia UL***
☐Hypoaesthesia LL**** ☐ Sensory Levels ☐ Paraesthesia ☐Urge-incontinence ☐ Incontinence

Diagnosis date : / /
☐CMI (Tonsillar herniation : ☐ <3mm ☐ 3-4mm ☐ ≥5mm)
☐CMII (Myelomeningocele: ☐YES ☐ NO)
☐Chiari Syndrome
☐ Primary Syringomyelia ☐Idiophatic Syringomyelia ☐Secondary Syringomyelia
(level: ☐cervical ☐dorsal ☐cervical-dorsal)
☐Syringobulbia
☐Hydromyelia (level: ☐cervical ☐dorsal ☐cervico-dorsal)
☐Hydrocephalus ☐ TCS ☐ Occult TCS ☐Retroflexed Odontoid ☐ Klippel-Feil

*Unemployed person, retired persons, students; **PFD: Posterior Fossa Decompression;
*** UL: upper limbs; ****LL: lower limbs; ***** MTN: motoneuron

Figure 1
Dedicated clinical Consortium form developed by the Interregional Chiari and Syringomyelia Consortium, including medical hystory, familial, radiological, clinical and diagnostic data.

The etiology of CM1 malformation is, at present, poorly understood. In some cases, CM1 may be associated with connective tissue diseases like Ehlers-Danhlos [22]. In the remaining cases, a multifactorial inheritance is the most likely explanation of the disease. Recently, a role for genetic factors in the disease pathogenesis has been suggested.

In CM patients, recent studies have revealed the presence of a small posterior fossa (PF) leading to a cramped cerebellum and herniation of the tonsils into the top of the spinal column. Based on examination of skull radiographs, Aydin *et al.* found that the posterior fossa was smaller and shallower in patients with CM1 malformation than in controls; the ratio of the posterior fossa with supratentorial volumes on MR images is smaller in CM1 patients than in controls, and those with smaller posterior fossa developed symptoms earlier and were more likely to respond to decompressive surgery. Experimentally-induced small posterior fossa was also found to lead to tonsillar herniation. So, it

Table 3
Summary of demographic and clinical data (gender, age, occupational status, surgery) in all patients and in CM/Syr patient groups; percentages in brackets

		Patient Group		
		All	CM[a]	Syr[a]
		n = 436	n = 347	n = 217
Gender (%)	M	144 (33)	111 (32)	78 (36)
	F	292 (67)	236 (68)	139 (64)
Occupational status (%)	Employed	192 (44)	132 (38)	111 (51)
	Unemployed[b]	244 (56)	215 (62)	106 (49)
Age (%)	Pediatric (≤18 yrs)	70 (16)	69 (20)	24 (11)
	Adult (18-60 yrs)	283 (65)	215 (62)	145 (67)
	Over 60 yrs	83 (19)	63 (18)	48 (22)
Surgery (%)	Yes	113 (26)	107 (31)	67 (31)
	No	323 (74)	240 (69)	150 (69)

[a] CM/Syr patient group includes associated forms: 128 patients with CMI/II+Syr; [b] Unemployed person, retired persons, students. *Abbreviations* - CM: Chiari Malformation; Syr: Syringomyelia.

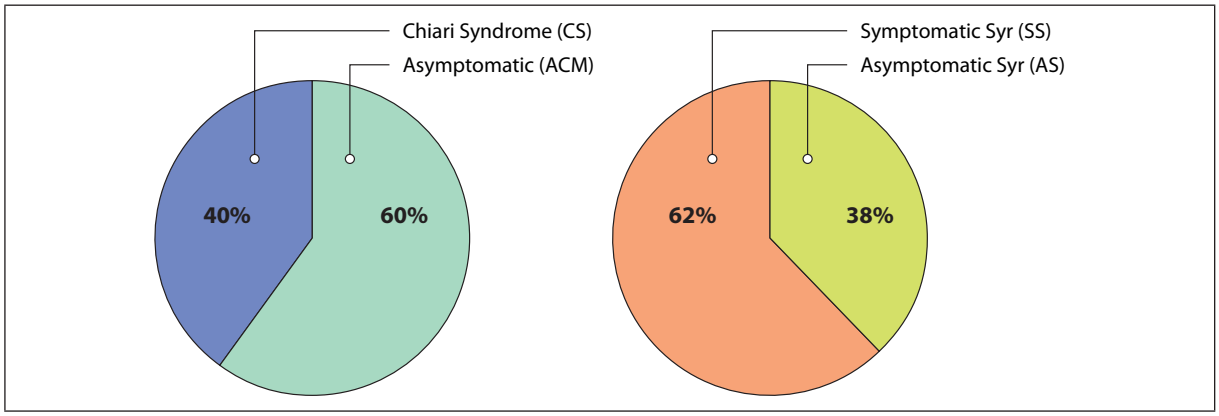

Figure 2
Percentages of symptomatic/asymptomatic forms in Chiari and Syringomyelia: SS are prevalent (62%) whereas CS are only 40%.

has been postulated that the pathogenesis of CM1 involves underdevelopment of the occipital bone, perhaps due to abnormal development of the occipital somite originating from the paraxial mesoderm, resulting in overcrowding in the posterior fossa [31]. In some families, the CM1-S phenotype is inherited as autosomal dominat trait. Genomewide linkage analyses of several families with CM1 identified candidate loci on chromosome 15q21.1-q22.3 (maximum 2-point nonparametric exponential lod score of 3.33 at rs744318) and on chromosome 9q22.31 (maximum multipoint parametric lod score of 3.05 between rs1000735 and rs2895201). Speer *et al.* postulated that an underlying gene responsible for CMI/Syr may have pleiotropic effects that influence posterior fossa volume, other skull bone abnormalities, the extent of cerebellar tonsil herniation, and the formation of Syr [32]. At present, however, the number and the type of genes involved in CM1 with or without Syr are unclear.

The indications, optimal timing, and type of surgical intervention to treat Syr associated with CM1 are unclear; prospective, controlled trials are lacking. Approximately 1/3 of untreated patients with Syr have minimal or no neurologic progression [33]. Progressive motor deficits and dysesthesias tend to respond more favourably to surgical intervention than sensory deficits. Greater syrinx size may predict a beneficial surgical response. Surgical intervention is suggested in patients with progressive motor deficits and a large syrinx. Suboccipital decompression, to alter the CSF flow and pressure dynamics, is considered the most successful technique [34, 35]. Williams advocate concurrent syringe-arachnoid shunting [36-38].

The strength of the study is that our estimations are based on a population based registry such as the Interregional Piemonte and Valle d'Aosta Rare Diseases Registry, integrated by the specific clinical Consortium form. A clear and standardized criteria for clinical inclusion was adopted.

Moreover, the dissemination of the shared recommendations has led to a greater awareness in the diagnostic process, especially improving its appropriateness of symptomatic versus asymptomatic forms.

A limitation of the study is the geographical local

Table 4
Demographic, radiological and prevalence/incidence data in CS and ACM patients

	Total CM (CM) n = 347	Symptomatic-Chiari Syndrome (CS) n = 139	Asymptomatic (ACM) n = 208
Age (%)	69 (20)	20 (29)	49 (71)
Pediatric (≤18 yrs)	215 (62)	87 (40)	128 (60)
Adult (18-60 yrs)	63 (18)	32 (51)	31 (49)
Over 60 yrs			
Gender (%)			
Male	111 (32)	52 (47)	59 (53)
Female	236 (68)	87 (37)	149 (63)
MRI Morphology (%)			
Tonsillar herniation ≥5mm	323 (93)	137 (42)	186 (58)
Tonsillar herniation 3-4mm	14 (4)	12 (17)	2 (83)
Tonsillar herniation ≤3 mm	10 (3)	0	10 (100)
Types (%)			
CMI A - CMI+Syr	125 (36)	75 (60)	50 (40)
CMI B-isolated	201 (58)	50 (25)	151 (75)
CMII + Myelomeningocele [a]	4 (1)	4 (100)	0 (0)
Other associated conditions [b]	17 (5)	10 (59)	7 (41)
Prevalence [c] [x100 000] and relative 95% Confidence Intervals	7.74 (6.965-8.596)	3.10 (2.625-3.659)	4.64 (4.049-5.313)
Gender			
Male	5.13 (4.260-6.177)	2.40 (1.833-3.151)	2.73 (2.114-3.517)
Female	10.17(8.952-11.55)	3.75 (3.039-4.624)	6.42 (5.469-7.537)
Age			
Pediatric (≤18 yrs)	9.42 (7.441-11.951)	2.73 (1.767-4.216)	6.69 (5.058-8.839)
Adult (18-60 yrs)	8.74 (7.650-9.992)	3.54 (2.868-4.363)	5.21 (4.378-6.188)
Over 60 yrs	4.87 (3.810-6.235)	2.47 (1.754-3.495)	2.40 (1.690-3.404)
2011 Incidence [d] [x100 000] and relative 95% Confidence Intervals	3.08 (2.605-3.635)	1.23 (0.942-1.596)	1.85 (1.493-2.294)
Gender			
Male	2.36 (1.793-3.099)	1.25 (0.858-1.816)	1.11 (0.745-1.650)
Female	3.75 (3.039-4.624)	1.21 (0.835-1.744)	2.54 (1.971-3.279)
Age			
Pediatric (≤18 yrs)	4.09 (2.868-5.844)	1.09 (0.553-2.154)	3.00 (1.983-4.546)
Adult (18-60 yrs)	3.54 (2.868-4.363)	1.47 (1.057-2.027)	2.07 (1.577-2.727)
Over 60 yrs	1.62 (1.063-2.484)	0.85 (0.475-1.524)	0.77 (0.420-1.424)

[a]CMII + Myelomeningocele: 75% of patients present also Syr; [b]Other associated conditions: 41% Retroflexed Odontoid, 24% Hydrocephalus, 24% Klippel-Feil, 11% TCS; [c]Prevalence cases/100 000 population who were alive in 2011 (ISTAT data); [d]New reported cases /100 000 population who were alive in 2011 (ISTAT data).
Abbreviations - CM: Chiari Malformation; Syr: Syringomyelia; TCS: Tethered Cord Syndrome.

extension of the census, restricted to only a few Italian regions (Piemonte and Valle d'Aosta), but with standardized access to the Syr and CM diagnosis and with availability of epidemiological data, also for Syr, included in the registry. More analytic and association analyses will need to be performed in the future.

CONCLUSIONS

The systematization of few known facts and the dissemination of guidelines or, failing these, of recommendations, as the result of a rational consensus by experts, represents a valuable tool for knowledge transfer drawn from biomedical and social and healthcare practices. We propose: adoption of Consortium Recommendations at national level to standardize the accessibility to the diagnosis and care process; moreover, the extend the methodology of census study in the national context to complete Italian epidemiologic data on Chiari and Syr. The estimated prevalence at national level could have a great impact in the field of rationalization of diagnostic costs and reduction of unnecessary hospitalizations/surgeries. We believe shared Interregional

Table 5
Demographic, radiological and Prevalence/Incidence data in Symptomatic Syr (SS) and in Asymptomatic Syr (AS) patients

	Total (Syr) n = 217	Symptomatic Syr (SS) n = 135	Asymptomatic (AS) n = 82
Age (%)	24 (11)	9 (37)	15 (63)
Pediatric (≤18 yrs)	145 (67)	96 (66)	49 (34)
Adult (18-60 yrs)	48 (22)	30 (62)	18 (38)
Over 60 yrs			
Gender (%)			
Male	78 (36)	50 (64)	28 (36)
Female	139 (64)	85 (61)	54 (39)
MRI Morphology (%)			
Syr	158 (73)	123 (78)	35 (22)
Hydro	59 (27)	12 (20)	47 (80)
MRI Distribution (%)			
Syringobulbia	2 (1)	2 (100)	0
Syr/Hydro cervical	54 (25)	33 (61)	21 (39)
Syr/Hydro thoracic	52 (24)	12 (23)	40 (77)
Syr/Hydro cervical-thoracic	109 (50)	88 (81)	21 (19)
Aetiology (%)			
Type I-primary Syr	128 (59)	95 (74)	33 (26)
Type II-idiopathic Syr	20 (9)	10 (50)	10 (50)
Type III-secondary Syr	30 (14)	23 (77)	7 (23)
Type IV - pure Hydro	39 (18)	7 (18)	32 (82)
Prevalence[a] [x100 000] and relative 95% Confidence Intervals	4.84 (4.124-5.527)	3.01 (2.544-3.563)	1.83 (1.473-2.269)
Gender			
Male	3.60 (2.889-4.499)	2.31 (1.753-3.046)	1.29 (0.895-1.870)
Female	5.99 (5.073-7.071)	3.66 (2.962-4.528)	2.33 (1.783-3.036)
Age			
Pediatric (≤18 yrs)	3.28 (2.201-4.873)	1.23 (0.646-2.334)	2.05 (1.240-3.378)
Adult (18-60 yrs)	5.90 (5.012-6.937)	3.90 (3.197-4.767)	2.00 (1.507-2.634)
Over 60 yrs	3.71 (2.801-4.923)	2.32 (1.626-3.313)	1.39 (0.881-2.201)
2011 Incidence[b] [x100 000] and relative 95% Confidence Intervals	0.82 (0.599-1.137)	0.51 (0.342-0.770)	0.31 (0.186-0.5524)
Gender			
Male	0.60 (0.351-1.028)	0.46 (0.251-0.851)	0.14 (0.047-0.408)
Female	1.03 (0.695-1.539)	0.56 (0.327-0.958)	0.47 (0.265-0.849)
Age			
Pediatric (≤18 yrs)	0.82 (0.375-1.786)	0.14 (0.024-0.773)	0.68 (0.291-1.597)
Adult (18-60 yrs)	1.06 (0.722-1.549)	0.81 (0.526-1.256)	0.25 (0.112-0.532)
Over 60 yrs	0.39 (0.165-0.906)	0.16 (0.042-0.564)	0.23 (0.079-0.682)

[a] Prevalence cases/100 000 population who were alive in 2011 (ISTAT data); [b] New Reported cases /100 000 population who were alive in 2011 (ISTAT data);
Abbreviations: *Syr* - Syringomyelia; *Hydro* - Hydromyelia.

Recommendations will help the promotion of national/international clinical research, i.e. multi-center prospective study to evaluate surgery efficacy in different clinical phenotypes (CMI with or without Syr/HDCT/TCS).

Finally, the design and the implementation of a specific registry dedicated to Syr and CM will contribute to better understanding the natural history of patients affected by these conditions. In fact, the European Commission is supporting European Reference Networks for implementing new registries on RDs. The collaboration and the strong linkage of activities at regional level with other initiatives at European level, such as European Reference Networks, will provide additional opportunities in the research and clinical aspect of Syr and CM.

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Authors' contributions statement

PC: study design, focus group analysis, data interpretation, literature analysis, draft and final revision of the manuscript. DG, PP: data collection, focus group analysis, final revision. GP, LM, LV: final revision of the manuscript. GM: study design and statistical analysis. SB, DR: literature analysis, data collection, final revision. YK: data interpretation, collaboration to the preparation and final revision of the manuscript. DT: data collection, literature analysis, final revision of the manuscript. The authors read and approved the final manuscript.

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