CHIARI MALFORMATION AND SLEEP-RELATED BREATHING DISORDERS.

Y. Dauvilliers, MD, PhD,[1,2] V. Stal, [3] MD; B. Abril MD,[1] P Coubes MD, PhD[6] S. Bobin, MD,[5] J. Touchon MD,[1,2] P. Escourrou, MD, PhD;[3] F. Parker, MD,[4] P. Bourgin, MD, PhD[3,7]

[1]Service de Neurologie, Hôpital Gui-de-Chauliac, [2]INSERM E0361, Montpellier, France
[3] Sleep laboratory, Hôpital Antoine Béclère, 92141 Clamart, Paris XI University, France
[4] Neurosurgery department, Hôpital Bicêtre, 94275 Le Kremlin-Bicêtre, Paris XI University, France
[5] Department of Oto-Rhino-Laryngology, hôpital Bicêtre, 94275 Le Kremlin-Bicêtre, Paris XI University, France
[6]Service de Neurochirurgie B, Hôpital Gui-de-Chauliac, Montpellier, France
[7] present address: Department of Biological Sciences and Department of Psychiatry, Stanford University, Stanford, CA 94305, USA

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Address correspondence to:

Patrice Bourgin, MD, PhD
Dept of Biological Sciences and Dept of Psychiatry, Stanford University,
371 Serra Mall, Stanford, CA 94305-5020
Tel: 650-723-5882; Fax: 650-725-5356
bourgin@stanford.edu

Yves Dauvilliers, MD, PhD
y-dauvilliers@chu-montpellier.fr

Abstract

Objective: To estimate the frequency, mechanisms, and predictive factors of sleep apnea syndrome (SAS) in a large group of children and adults affected with type I and II chiari malformation (CM).
Background: The anatomical and functional integrity of both respiratory circuits and lower cranial nerves controlling the upper airway is necessary for breathing control during sleep. These latter structures may be altered in CM, and a few investigations have reported CM-related sleep disordered breathing.
Methods: Forty-six, consecutive, unrelated CM patients (40 CMI, 6 CMII), of which 20 were children (8 male) and 26 were adults (12 male), underwent physical, neurological, oto-rhino-laryngoscopic examination, MRI, and polysomnography.
Results: SAS was present in 31 (67.4%) of the CM patients (70% of CMI, 50% of CMII, including mainly children). Sixty percent of children with CM exhibited SAS, including 35% with obstructive (OSAS) and 25% with central (CSAS) sleep apnea syndrome. SAS was observed in 73% of CM adults (57.7 % OSAS, 15.4% CSAS). Severe SAS was found in 23% of CM adults. Multiple regression analysis revealed that age, type II Chiari and vocal cord paralysis predicted the central apnea index.
Conclusion: SAS is highly prevalent in all age groups of patients suffering from CM. CSAS, a rare condition in the general population, was common among the CM patients in our study. SDB associated with CM may explain the high frequency of respiratory failures observed during curative surgery of CM. Our results suggest that SAS should be systematically screened in CM patients, especially before surgery.

Chiari malformation (CM) is characterized by herniation of the cerebellum with variable extent through the foramen magnum (CM type I, and II with more severe malformation) and can be associated with myelomeningocele and myelodysplasia, resulting in different clinical presentations.[1] CM type I is defined by a herniation of medulla and cerebellar tonsils, while CM type II is also characterized by a caudal displacement of the vermis. CM can also be associated with basilar invagination (defined as violation of at least 6.6 mm of the Chamberlain line by the axis odontoid process) that leads to a smaller volumetric capacity of the posterior fossa. With the development of brain imaging techniques, especially magnetic resonance imaging (MRI), the identification of CM based on objective anatomic criteria has become more frequent and more precise with clinical and prognostic relevance.[2] Sleep-disordered breathing (SDB) is a chronic and highly prevalent condition among adults, and is associated with disruption of sleep continuity and intermittent hypoxemia, with important adverse health-related consequences.[3,4] In contrast, childhood SDB is rare and the criteria for diagnosis differ from those used in adults. [3-5]

Respiration is controlled by an automatic respiratory mechanism that is subject to continuous voluntary intervention in the waking state. During sleep, the automatic respiratory control is critical since the voluntary system of breathing control is not functional. Automatic breathing mechanisms require the integrity of the brainstem which is the primary source of both, ventilatory pattern generation and processing of respiratory afferent input from peripheral arterial and central chemoreceptors, as well as intrapulmonary and upper airways receptors. The efferent nervous pathways involve the IX and X pairs of cranial nerves and muscles dedicated to inspiration and expiration. As CM-related herniation may result in compression of the afferent, efferent and/or central respiratory generator within the brainstem, one may hypothesize that sleep apnea syndrome (SAS) of various mechanisms may be frequently observed in CM. Accordingly, the association between CM and SAS has been previously described in case report studies[6-10] ranging from acute respiratory failure to central and obstructive apneas and hypopneas during sleep. Only one study of 23 CM-affected patients included a control group[11]. In this latter report including only adults and CM type I, the presence of SAS (defined as apnea/hypopnea index values greater than 5) was observed in 44% and 60% of CMI patients, respectively with and without syringomyelia, therefore higher than in the control group with 12% of patients affected.[11] Another recent study on 16 adults affected with CM type I reported the presence of SAS (defined as apnea/hypopnea index values greater than 10) in 75% of cases[12]. In both studies, central apneic events were frequent, from 17.6% to 48% of cases.[11 12]. However, because of the low sample size and few studies reported, additional data are needed in order to further describe the frequency, severity, and pathophysiological mechanisms underlying those respiratory disturbances, especially in adults affected with CM type II and in children.. Moreover, predictive factors for SAS in Chiari affected patients have not yet been identified.

In the current study, we report on the occurrence, mechanisms and severity of sleep disordered breathing in 46 consecutive infant and adult CM type-I and II-affected patients. In addition, we investigated whether clinical or radiological findings impacted the sleep respiratory events index.

METHODS

Patients

We studied 46 consecutive unrelated patients affected with CM that were seen in 2 different centers (n= 24 from the Montpellier Sleep Wake Disorders Center- Center 1; and 22 from the Paris-Antoine-Béclère Sleep Wake Disorders Center - Center 2). All patients were referred to our neurology or neurosurgery departments for symptoms of craniocervical junction

malformation. The only inclusion criterion was the presence of CM assessed by brain MRI, independent of the severity of clinical symptoms or complaints. Exclusion criteria were the presence of a concomitant neurological disorder, a previous cranial or cervico-vertebral surgery, a tonsillar hypertrophy (in case of children) and an advanced congestive heart failure. Patients included were recruited over 5 years and ranged from 4 to 64 years of age with 20 children and 26 adults. Patients were divided into three age groups at the time of the evaluation: Group 1 (≤ 18 years old, y.o.), Group 2 (19 to 30 y.o.), and Group 3 (older than age 30).

All patients underwent physical, neurological and oto-rhino-laryngoscopic examination (including fiberoptic laryngoscope), MRI, and polysomnography (PSG). Clinical, radiological and sleep variable evaluations were comparable in both centers. None of the patients were taking any psychotropic medication or other medication known to influence sleep and/or sleep disorders breathing.

The protocol was approved by research scientific committee on both hospitals. All patients accepted the project and gave their informed consent to participate.

Procedures:

Clinical data

Clinical symptoms related to cranio-vertebral junction compression, cerebellar dysfunction, central cord and cranial nerves disturbances and pain were systematically noted. A systematic interview about sleep-related disorders was realized that mainly focus on excessive daytime sleepiness. Sleepiness was estimated with the Epworth Sleepiness Scale (ESS)[13] in patients above 16 y.o. and was considered abnormal when ESS score was above 10.

Radiological data

All patients underwent the same MRI protocol with 1.5 T sagittal-axial T1-T2 sequences brain and cervicothoracic spine. CMI was defined as tonsillar herniation to a point at least 5 mm below the foramen magnum on midsagittal T1 sequence.[1 2 14] CMII was defined as tonsillar plus vermis herniations associated with myelodysplasia, myelomeningocele and frequently hydrocephalus. Basilar impression was defined as violation of at least 6.6 mm of the Chamberlain line by this axis odontoid process. Syringomyelia or bulbia were defined as spinal or medulla cord cavity with contents similar to CSF on T1-T2 sequences.

Sleep variables

All patients underwent a full-night audio-PSG in a sleep laboratory, that included recordings of electroencephalograms (C4-A1, C3-A2), electrooculograms, chin electromyograms, oronasal airflow, thoraco-abdominal movements, pulse oximetry, leg movements and electrocardiogram. Oronasal airflow was measured by a thermistor in 15 children (i.e. less than 15 y.o.) and with nasal pressure cannula in the remaining 31 patients. Sleep stages, arousals and respiratory events were scored manually in accordance with international procedures and current guidelines.[5 15-17]

Obstructive sleep apneas were defined as a complete cessation of airflow for more than 10 s associated with thoraco-abdominal movements. Central sleep apneas were defined by the absence of airflow and thoraco-abdominal movements for more than 10 s for adults, and for more than 20 s or longer than 10s and associated with a 3% drop in oxyhemoglobin desaturation (SaO2) for children. Mixed apnea was defined as initial central apnea followed by obstructive apnea. Hypopneas were defined as a reduction of at least 50% in airflow that was associated with a 3% drop in SaO2 and/or a micro-arousal. Adult patients with more than 20% of respiratory events of central origin underwent a second PSG with measurement of respiratory efforts by oesophageal pressure to formally differentiate central from obstructive respiratory events. The diagnostic criteria for central apnea was the absence of airflow and thoraco-abdominal wall movement occurring simultaneously with the lack of intrathoracic

pressure swings. Criterion to differentiate central and obstructive hypopneas was a reduction of oesophageal pressure swing in proportion with the reduction in airflow. In addition, the ventilatory response to CO2 was conducted in adult patients with central events.

The apnea/hypopnea index (AHI) was calculated as the number of episodes of apnea and hypopnea per hour of total sleep time. Sleep apnea syndrome (SAS) was defined as an AHI ≥ 5 in adults and ≥ 1 in children regardless of the presence of related clinical symptoms.[3] The diagnosis of central sleep apnea syndrome (CSAS) was made when more than 50% of apneic events were central.[3] The diagnosis of severe SAS was defined as AHI ≥ 30 in adults and ≥ 10 in children.

Statistical analysis

Values for the parameters are presented as mean ± sem. Statistical analyses were performed using StatView 5.0.1. and SigmaStat 3.0. To evaluate differences between the two centers, t-tests for independent samples for the continuous variables and Pearson X^2 tests for the dichotomous variables were used. To evaluate age category-related differences, we used Pearson X^2 tests for the dichotomous variable and one-way ANOVA followed by Post hoc Tukey highly significant difference (HSD) tests for continuous variables. Multiple linear regression analysis was conducted including age, BMI, Chiari type, sensory loss, pyramidal signs, cerebellar signs, vocal cord paralysis with obstructive apnea index (OAI) or central apnea index (CAI) as the dependent variable. This latter analysis included a restricted number of factors regarding the sample size of the population and these factors covered a large spectrum (epidemiology, neurological syndrome, upper airway control) of most relevant data.

RESULTS

Clinical features

Table 1 presents clinical and radiological data by age of the patients at the time of the PSG. We noted a significant age difference between patients studied at the two sites (mean age at 16.2 ± 15.4 in Center 1 and 37.3 ± 13.3 in Center 2) due to recruitment bias. Regarding neurological symptoms, chronic pain was the most common complaint in CM population (95% of adults), mainly characterized by neck and limb extremity pain and recurrent headaches. The presence of pain, motor weakness and lower cranial (IX and X) nerves palsies increased with advancing age (Table 1). Among sleep-related problems, a complaint of excessive daytime somnolence (EDS) was present in 26.1% of CM patients and in 42.3% of adults. In addition, 34.5% of patients above 16 y.o. had an ESS score above 10. Snoring was noted in 56.5% of CM patients and 73% in adults.

Table 1: Clinical and MRI data of 46 patients with Chiari malformation divided into three age groups

Characteristics	≤ 18 years n = 20	19-30 years n = 10	≥ 31 years n = 16	p
Male/female ratio	8/12	6/4	6/10	ns
Chiari malformation I/II ratio	15/5	10 /0	15/1	<0.005
EDS, (%)	5	20	56	<0.001
Snoring, (%)	35	80	69	ns
BMI	19.1 ± 1.0	23.4 ± 1.8	26.9 ± 1.4	<0.001
Neurological symptoms				
Pain, %	45	100	94	<0.001
Motor weakness, %	25	60	75	<0.01
Cerebellar signs, %	20	20	31	ns
Dizziness, %	0	20	12	ns
Nystagmus, %	10	20	25	ns
Vocal cord paralysis, %	0	10	19	ns
Trigeminal sensory loss, %	0	10	25	ns
IX and/or X palsies, %	10	70	19	<0.01
Sensory loss, %	55	70	56	ns
Impaired deep sensibility, %	0	20	19	ns
Pyramidal tract signs, %	20	40	44	ns
MRI findings				
Basilar impression, %	10	60	10	<0.001
Syringomyelia, %	65	60	56	ns

EDS: presence of excessive daytime sleepiness
BMI: Body Mass Index
Patients ranged from 4 to 64 years of age. Analysis of the effect of age class group on continuous variable has been tested by one way ANOVA with corresponding p significance. Pearson X^2 tests have been used for dichotomous variables.

Radiological findings

Forty patients presented with type I CM, and six with type II. Only one adult in our study was diagnosed with CMII (Table 1). The CMII/I ratio significantly decreased with age. Twenty-eight (61%) patients had an associated syringomyelia, nine had a basilar impression, and two CMI adults had a syringobulbia.

Sleep analysis

Table 2 shows PSG results relative to age of patients at time of study. As expected, total sleep time and slow wave sleep amounts clearly decreased with age class. The complaint of chronic pain did not explain the low sleep efficiency and percentage of slow wave sleep. A SAS was present in 31 of the 46 (67.4%) CM patients, including 28 of the 40 (70%) CMI patients and three of the six (50%) CMII patients. There was no sex difference in the frequency of SAS in both children and adults. SAS was observed in 91.7% of patients complaining of EDS and in 58.8% of patients without ($p= 0.037$).

Sixty percent of the children population presented with SAS including 35% with obstructive SAS and 25% with central SAS. Three children affected with both CMII and SAS had CSAS. None of children were affected with severe SAS. Regarding sleep-related symptoms, 91.7% of the seven children with snoring had a SAS. Maximal duration of an obstructive event was 68 s (patient aged 7 y.o.) and 30 s for a central event (patient aged 8 y.o.). Finally, mean SaO2 was above 96% but its minimum and percentage of time spent below 90% were clearly abnormal (Table 2).

The prevalence of sleep apnea syndrome was 73% in the adult group, including 57.6 % with OSAS and 15.4% with CSAS. Severe SAS was observed in 23%, with severe OSAS in five cases (19.2%) and severe CSAS in one case (3.8%). OSAS frequency and obstructive apnea index (OAI) are significantly increased in the older age group ($\geq$ 31 years old; Table2). Mean SaO2 as well as percentage of sleep time with SaO2 below 90% are significantly decreased in the same age range. CSAS was reported in 9 CM patients (19.6%) with only one patient with severe CSAS (aged 56 y.o.) and abnormal ventilatory response to CO2. In addition, two females with CMI also presented a central alveolar hypoventilation diagnosis characterized by prolonged elevation of PaCO2 greater than 45 mmHg during sleep. One 39 y.o. had a normal BMI and a severe OSAS (40/h), and the other 43 y.o. had high BMI (39), normal lung function and no SAS. Both presented with abnormal ventilatory response to CO_2.

Table 2: Polysomnographical data of 46 patients with Chiari malformation divided into three age groups

Characteristics	≤ 18 years n = 20	19-30 years n = 10	≥ 31 years n = 16	P
Polysomnography				
Total sleep time	481.9 ± 21.5	395.8 ± 30.2	313.7 ± 21.	<0.001
Sleep onset latency	20.8 ± 4.3	23.0 ± 7.7	18.7 ± 6.3	ns
% Sleep efficiency	89.1 ± 3.0	74.8 ± 7.8	76.8 ± 3.6	0.05
% Stage 2	47.0 ± 2.1	55.2 ± 1.9	54.3 ± 3.6	ns
% SWS	26.2 ± 1.4	18.9 ± .9	18.8 ± 1.7	<0.005
% REM	19.5 ± 1.3	16.3 ± 2.3	11.5 ± 1.5	<0.01
SAS diagnosis				
SAS, (%)	60	60	81	0.05
OSAS, (%)	35	40	69	<0.01
Severe OSAS, (%)	0	0	31	<0.05
CSAS, (%)	25	20	13	ns
Severe CSAS, (%)	0	0	6	ns
Respiratory events				
AHI	2.6 ± 0.5	5.64 ± 1.6	26.4 ± 6.6	<0.001
OAI	0.2 ± 0.07	0.48 ± 0.2	6.7 ± 2.4	<0.005
HI	1.6 ± 0.4	3.84 ± 1.5	16.4 ± 4.6	<0.005
CAI	0.8 ± 0.2	1.31 ± .8	3.3 ± 1.7	ns
O_2 saturation				
O_2 mean saturation	97.0 ± 0.2	96.15 ± 0.4	92.9 ± 0.9	<0.001
O_2 min saturation	84.7 ± 2.1	89.08 ± 1.6	80.7 ± 2.7	ns
TTS (%) with SaO_2 <90%	1.0 ± 0.5	0.4 ± 0.3	13.1 ± 5.3	0.05

SWS: Slow wave sleep
REM: Rapid eye movements
OSAS: Obstructive sleep apnea syndrome
CSAS: Central sleep apnea syndrome
SAS: Sleep apnea syndrome
AHI: Apnea hypopnea index

OAI: Obstructive apnea index
HI: Hypopnea index
CAI : Central apnea index
Results are expressed as mean ± sem or %
TTS (%) with SaO_2 <90%, mean ± sem: percentage of sleep time spent with SaO2 below the threshold of 90%. We used this latter criterion as an indicator of SAS severity. The value for each patient corresponds to drops of SaO2 below 90% following apneic events with return to normal SaO2 after the drop. It also corresponds to long sustained desaturations below 90% for two of them who were also presenting with central alveolar hypoventilation.
Analysis of the effect of age class group on continuous variable has been tested by one way ANOVA with corresponding p significance. Pearson X^2 tests have been used for dichotomous variables.

Predictive factors for central apnea index (CAI) and obstructive apnea index (OAI)
We conducted a multiple regression analysis that included age, BMI, Chiari type and clinical findings with index of respiratory events during sleep as the dependent variable. The multiple regression analysis was conducted separately with CAI and OAI as dependent variables. Considering CAI, our analysis revealed that a statistically significant proportion of the variance was accounted for by age, Chiari type II, and vocal cord paralysis but not by the neurological parameters (Table 3). Only the age appeared to account for the ability to predict OAI (p=0.041).

Table 3: Multiple linear regression analysis investigating predictors of Central Apnea Index (CAI)

	Coefficient	Std. Error	t	P
Age	0.0736	0.0353	2.087	0.044
BMI	-0.0562	0.0974	-0.577	0.567
Chiari type	3.962	1.534	2.582	0.014
Sensory loss	-0.187	1.036	-0.180	0.858
Pyramidal signs	-0.673	1.070	-0.629	0.533
Cerebellar signs	2.242	1.195	1.877	0.068
Vocal cord paralysis	7.805	1.816	4.298	<0.001

DISCUSSION

This is one of the largest reports on sleep-disordered breathing in CM. The frequency of SAS observed in our patient population is extremely high in comparison with the general population: 67.4% of patients were diagnosed with SAS, of which 70% were type I CM and 50% were type II (including mostly children). SAS is rare in childhood, with a prevalence of approximately 1-3%,[3 18-20] in contrast to the 60% of CM children in the present study. Estimates of SAS prevalence among adults in the general population vary based on the population studied and the inclusion criteria, but range from 4 to 15 % in men and 2 to 9 % in women[3 4 21-24]. To compare more specifically to our adult population of CM patients, the prevalence ranks from 2.4 to 17% among subjects between 19 to 65 years old, and from 2 to 17% among those aged range subjects with a BMI between 28 to 32 kg/m2.[23 24]

In contrast, 73% of CM adults in the present study, with a mean age of 38.7 ± 13.8 and a mean BMI of 25.6 ± 5.9, presented with SAS, including 13% that had severe SAS. We observe a male/female ratio (1.22:1), similar to prior studies, but it is strongly attenuated as probably most of the SAS are a consequence of CM.

There are several limitations to the present study. First, there was no control group because the inclusion of matched-control subjects was almost impossible since patients affected with chronic pain are generally not referred to a neurology/neurosurgery department. The main factors influencing prevalence of SDB are age, BMI, sex and AHI cut-off. Regarding these factors our population is comparable to the data available in the literature, especially in adults the data from the two larger cohort studies from Wisconsin and Pennsylvania. Moreover, our results demonstrate that SAS is highly prevalent in CM patients compared with what has been demonstrated in the literature. Second, we did not perform a systematic assessment of end-tidal CO2 in children. Third, a definitive diagnosis of a central sleep event theoretically requires oesophageal pressure monitoring, which is rarely done in children. Finally, the partial use of thermistor (and not only nasal cannula) in most of children to assess mouth and nasal airflow was another limit of the present study. However, that procedure was explained by a five year recruitment period and thermistor was still frequently used for the assessment of normal reference values of SDB in children[25 26]

The pathophysiological mechanisms underlying SAS in CM remain unclear . The extremely high frequency of SAS in CM reported by our and others[6-12] may be explained by the anatomical localization of respiratory centers and pathways within the brainstem and their possible injury in CM. In the literature, patients with predominantly central apneas are rarely seen,[22] and most patients with central apneas also have some obstructive events as observed in our population. We found that vocal cord paralysis which is a sign of impairment in upper airway control, account for the ability to predict index of respiratory events of central origin. This data confirm that a laryngoscopic examination is systematically required in CM patients, especially among those presenting with SAS or with a stridor (sometimes misinterpreted with snoring). We also report that type II CM was a predictive factor of higher CAI, therefore serving as an anatomic individualized risk factor in relation with different degree and site of brainstem compression. Interestingly, BMI do not account for the ability to predict respiratory events index in CM patients which provide indirect evidence for a causal relation between CM and SDB in our population.

The mechanisms responsible for the different types of apneas likely overlap with the evidence of pharyngeal airway narrowing during purely central apneas.[27] The occurrence of central apneas, central alveolar hypoventilation, or both might be the consequence of an alteration of the chemoreflex. Obstructive events due to pharyngeal collapse may be related to alteration of the innervation of the upper airway (mainly 9 and 10th cranial nerves) and may also trigger central apneas.[27] It is also unclear whether central apneas are a consequence of a dysfunction

or lesion (infarction or hemorrhages due to the compression) of the central respiratory components. Interestingly, three adults presenting with SAS (2 CSAS, 1 OSAS) displayed medulla MRI signal abnormalities suggestive of ischemic lesions.

Surgical decompression is proposed as the treatment of choice for SDB in CM patients and, at least, one third of CM patients enrolled in the present study underwent surgery. The effect of surgery however, differs among patients, and respiratory failure is a frequent complication of the treatment.[1 6 8 9 28-32] Nocturnal respiratory depression was noted in 14% of operated patients in the study of Paul and coll.[1], usually within the first five days after surgery, and was supposed to be ascribed to edema formation. Moreover, the incidence of respiratory arrest and death during sleep has been reported to be increased in CM patients.[6 12 28] Therefore, sleep disordered breathing in patients suffering from CM might be a cause of mortality.[6 12 28-32] The high prevalence of SAS reported in our study indicates that respiratory disturbances during sleep should be systematically screened in CM patients in order to prevent the risk of respiratory failure associated with surgery, especially by use of mechanical ventilation for the post-operative period. Finally, post-surgical PSG studies are needed in order to determine whether treatment of SAS may improve the risk of respiratory failure during surgery and mortality associated with CM.

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