PAPER

Chiari malformation and sleep related breathing disorders

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Objective: To estimate the frequency, mechanisms and predictive factors of sleep apnoea syndrome (SAS) in a large group of children and adults with type I (CMI) and II (CMII) 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 patients with CM (40 CMI, six CMII), of which 20 were children (eight males) and 26 were adults (12 males), underwent physical, neurological and oto-rhino-laryngoscopic examination, MRI and polysomnography.
Results: SAS was present in 31 (67.4%) of the patients with CM (70% of CMI, 50% of CMII, including mainly children). Sixty per cent of children with CM exhibited SAS, including 35% with obstructive (OSAS) and 25% with central (CSAS) sleep apnoea 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 apnoea 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 patients with CM in our study. Sleep disordered breathing 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 for in patients with CM, especially before surgery.

Chiari malformation (CM) is characterised 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 herniation of the medulla and cerebellar tonsils, while CM type II is also characterised by 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 MRI, identification of CM based on objective anatomical 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 hypoxaemia, 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 as 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 hypothesise that sleep apnoea syndrome (SAS) of various causes may be frequently observed in CM. Accordingly, the association between CM and SAS has been described previously in case report studies[6–10] ranging from acute respiratory failure to central and obstructive apnoeas and hypopnoeas 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 apnoea/hypopnoea index values greater than 5) was observed in 44% and 60% of CMI patients, respectively, with and without syringomyelia, and 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 apnoea/hypopnoea index values greater than 10) in 75% of cases.[12] In both studies, central apnoeic events were frequent (17.6–48% of cases).[11 12] However, because of the low sample size and few studies reported, additional data are needed 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 SDB in 46 consecutive infant and adult CM type I and II affected patients. In addition, we investigated whether clinical or radiological findings impacted on the sleep respiratory events index.

METHODS

Patients

We studied 46 consecutive unrelated patients affected with CM that were seen in two different centres (n = 24 from the Montpellier Sleep Wake Disorders Centre (centre 1) and 22

Abbreviations: AHI, apnoea/hypopnoea index; BMI, body mass index; CAI, central apnoea index; CM, Chiari malformation; CSAS, central sleep apnoea syndrome; ESS, Epworth Sleepiness Scale; OAI, obstructive apnoea index; OSAS, obstructive sleep apnoea syndrome; PSG, polysomnography; SAS, sleep apnoea syndrome; SDB, sleep disordered breathing

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

Characteristic	⩽18 years (n = 20)	19–30 years (n = 10)	⩾31 years (n = 16)	p Value
Sex (M/F 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

BMI, body mass index; EDS, excessive daytime sleepiness
Patients ranged from 4 to 64 years of age. Analysis of the effect of age group on continuous variable was tested by one way ANOVA with corresponding p significance values. Pearson χ^2 tests were used for dichotomous variables.

from the Paris-Antoine-Béclère Sleep Wake Disorders Centre (centre 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, previous cranial or cervico-vertebral surgery, tonsillar hypertrophy (in the case of children) and 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), group 2 (19–30 years old) and group 3 (>age 30 years old).

All patients underwent physical, neurological and oto-rhino-laryngoscopic examinations (including fibreoptic laryngoscope), MRI and polysomnography (PSG). Clinical, radiological and sleep variable evaluations were comparable in both centres. None of the patients was taking psychotropic medication or other medications known to influence sleep and/or SDB.

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

Procedures

Clinical data

Clinical symptoms related to cranio-vertebral junction compression, cerebellar dysfunction, central cord and cranial nerve disturbances and pain were systematically noted. A systematic interview on sleep related disorders was conducted that focused mainly on excessive daytime sleepiness. Sleepiness was estimated with the Epworth Sleepiness Scale (ESS)[13] in patients over 16 years of age and was considered abnormal when the ESS score was >10.

Radiological data

All patients underwent the same MRI protocol with 1.5 T sagittal–axial T1–T2 sequences of the brain and cervicothoracic spine. CMI was defined as tonsillar herniation to a point at least 5 mm below the foramen magnum on midsagittal T1 sequences.[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, thoracoabdominal movements, pulse oximetry, leg movements and ECG. Oronasal airflow was measured by a thermistor in 15 children (ie, <15 years of age) 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 apnoeas were defined as complete cessation of airflow for more than 10 s associated with thoracoabdominal movements. Central sleep apnoeas were defined by the absence of airflow and thoracoabdominal movements for more than 10 s for adults and for more than 20 s or longer than 10 s and associated with a 3% drop in oxyhaemoglobin desaturation (SaO_2) for children. Mixed apnoea was defined as initial central apnoea followed by obstructive apnoea. Hypopnoeas were defined as a reduction of at least 50% in airflow that was associated with a 3% drop in SaO_2 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 apnoea were the absence of airflow and thoracoabdominal wall movement occurring simultaneously with lack of intrathoracic pressure swings. The criterion to differentiate central and obstructive hypopnoeas was a reduction in oesophageal pressure swing in proportion to the reduction in airflow. In addition, the ventilatory response to CO_2 was conducted in adult patients with central events.

The apnoea/hypopnoea index (AHI) was calculated as the number of episodes of apnoea and hypopnoea per hour of total

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

Characteristic	⩽18 years (n = 20)	19–30 years (n = 10)	⩾31 years (n = 16)	p Value
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 (0.9)	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 (0.8)	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

AHI, apnoea hypopnoea index; CAI, central apnoea index; CSAS, central sleep apnoea syndrome; HI, hypopnoea index; OAI, obstructive apnoea index; OSAS, obstructive sleep apnoea syndrome; REM, rapid eye movements; SAS, sleep apnoea syndrome; SWS, slow wave sleep.
Results are expressed as mean (SEM) or %.
TTS (%) with SaO_2 <90%, mean (SEM): percentage of sleep time spent with SaO_2 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 SaO_2 below 90% following apnoeic events with return to normal SaO_2 after the drop. It also corresponds to long sustained desaturations below 90% for two patients who also presented with central alveolar hypoventilation.
Analysis of the effect of age group on continuous variables was tested by one way ANOVA with corresponding p significance values. Pearson χ^2 tests were used for dichotomous variables.

sleep time. 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 apnoea syndrome (CSAS) was made when more than 50% of apnoeic 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 centres, t tests for independent samples for continuous variables and Pearson χ^2 tests for dichotomous variables were used. To evaluate age category related differences, we used Pearson χ^2 tests for dichotomous variables and one way ANOVA followed by post hoc Tukey highly significant difference tests for continuous variables. Multiple linear regression analysis was conducted including age, body mass index (BMI), Chiari type, sensory loss, pyramidal signs, cerebellar signs and vocal cord paralysis with obstructive apnoea index (OAI) or central apnoea 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 the 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 at the two sites (mean age of 16.2 (15.4) years in centre 1 and 37.3 (13.3) years in centre 2) because of recruitment bias. Regarding neurological symptoms, chronic pain was the most common complaint in the CM population (95% of adults), mainly characterised 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 was present in 26.1% of patients with CM and in 42.3% of adults. In addition, 34.5% of patients older than 16 years had an ESS score >10. Snoring was noted in 56.5% of patients with CM and 73% in adults.

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 the age of the patients at the time of the study. As expected, total sleep time and slow wave sleep clearly decreased with age class. The complaint of chronic pain did not explain the low sleep efficiency and percentage of slow wave sleep. An SAS was present in 31 of the 46 (67.4%) patients with CM, including 28 of the 40 (70%) CMI patients and three of the six (50%) CMII patients. There was a difference in the frequency of SAS between the sexes in both children and adults. SAS was observed in 91.7% of patients complaining of excessive daytime somnolence and in 58.8% of patients without (p = 0.037).

Sixty per cent of the children presented with SAS, including 35% with obstructive SAS (OSAS) and 25% with CSAS. Three children affected with both CMII and SAS had CSAS. None of children was affected by severe SAS. Regarding sleep related

Table 3 Multiple linear regression analysis investigating predictors of central apnoea index

	Coefficient	SE	t	p Value
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

BMI, body mass index.

symptoms, 91.7% of the seven children with snoring had an SAS. Maximal duration of an obstructive event was 68 s (patient aged 7 years) and 30 s for a central event (patient aged 8 years). Finally, mean SaO_2 was greater than 96% but its minimum and percentage of time spent below 90% were clearly abnormal (table 2).

The prevalence of SAS 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 OAI were significantly increased in the older age group (⩾31 years old) (table 2). Mean SaO_2 as well as percentage of sleep time with SaO_2 below 90% were significantly decreased in the same age range. CSAS was reported in nine patients with CM (19.6%) with in only one patient with severe CSAS (aged 56 years) and abnormal ventilatory response to CO_2. In addition, two females with CMI also presented a central alveolar hypoventilation diagnosis characterised by prolonged elevation of $PaCO_2$ greater than 45 mm Hg during sleep. One 39 year old had a normal BMI and a severe OSAS (40/h), and the other 43 year old had a high BMI (39), normal lung function and no SAS. Both presented with an abnormal ventilatory response to CO_2.

Predictive factors for central apnoea index and obstructive apnoea index

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 neurological parameters (table 3). Only age appeared to account for the ability to predict OAI ($p = 0.041$).

DISCUSSION

This is one of the largest reports on SDB in CM. The frequency of SAS observed in our patient population was extremely high in comparison with the general population: 67.4% of patients were diagnosed with SAS, of whom 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 with 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 from 2% to 9% in women.[3 4 21–24] To compare more specifically to our adult population of patients with CM, the prevalence ranks from 2.4% to 17% among subjects between 19 and 65 years old, and from 2% to 17% among those of the same age with a BMI of 28–32 kg/m^2.[23 24]

In contrast, 73% of CM adults in the present study, with a mean age of 38.7 (13.8) years and a mean BMI of 25.6 (5.9) kg/m^2, presented with SAS, including 13% who had severe SAS. We observed a male/female ratio (1.22:1) similar to previous studies, but it was strongly attenuated as possibly most of the SAS were a consequence of CM.

There are several limitations to the present study. Firstly, there was no control group because the inclusion of matched control subjects was almost impossible as patients affected with chronic pain are generally not referred to a neurology/neurosurgery department. The main factors influencing the prevalence of SDB are age, BMI, sex and AHI cut-off. Regarding these factors, our population was comparable with the data available in the literature, especially the adult data from the two larger cohort studies from Wisconsin and Pennsylvania. Moreover, our results demonstrated that SAS was highly prevalent in patients with CM compared with that demonstrated in the literature. Secondly, we did not perform a systematic assessment of end-tidal CO_2 in children. Thirdly, 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 the children to assess mouth and nasal airflow was another limitation of the present study. However, the procedure is explained by a 5 year recruitment period and the use of a 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 us and others[6–12] may be explained by the anatomical localisation of respiratory centres and pathways within the brainstem and their possible injury in CM. In the literature, patients with predominantly central apnoeas are rarely seen,[22] and most patients with central apnoeas 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, accounts for the ability to predict the index of respiratory events of central origin. These data confirm that a laryngoscopic examination is systematically required in patients with CM, especially among those presenting with SAS or with a stridor (sometimes misinterpreted as snoring). We also report that type II CM was a predictive factor of higher CAI, therefore serving as an anatomical individualised risk factor in relation to different degrees and sites of brainstem compression. Interestingly, BMI does not account for the ability to predict respiratory events index in patients with CM which provide indirect evidence for a causal relation between CM and SDB in our population.

The mechanisms responsible for the different types of apnoeas likely overlap with the evidence of pharyngeal airway narrowing during purely central apnoeas.[27] The occurrence of central apnoeas, 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 IX and X cranial nerves) and may also trigger central apnoeas.[27] It is also unclear whether central apnoeas are a consequence of a dysfunction or lesion (infarction or haemorrhages caused by the compression) of the central respiratory components. Interestingly, three adults presenting with SAS (two CSAS, one OSAS) displayed medulla MRI signal abnormalities suggestive of ischaemic lesions.

Surgical decompression is proposed as the treatment of choice for SDB in patients with CM and, at least one third of patients with CM 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 colleagues,[1]

usually within the first 5 days after surgery, and was thought to be ascribed to oedema formation. Moreover, the incidence of respiratory arrest and death during sleep has been reported to be increased in patients with CM.[6 12 28] Therefore, SDB 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 for in patients with CM in order to prevent the risk of respiratory failure associated with surgery, especially by use of mechanical ventilation for the postoperative 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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