ORIGINAL ARTICLE



# Dynamic changes in sleep-related breathing abnormalities in bilateral paramedian mesencephalon and thalamus stroke: a follow-up case study

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#### Abstract

*Background* Bilateral paramedian thalamic stroke is characterized by hypersomnia, vertical gaze palsy, amnestic alteration, and apathic state. Combined lesion of the paramedian thalamus and mesencephalon bilaterally is extremely rare. Little is known about the breathing disturbances of the particular region due to the lesion. The following describes the specific case of a woman, age 62, with bilateral paramedian thalamic and mesencephalic stroke. Initially, the patient's complaints exhibited altered vigilance and vertical gaze palsy. Notably, following the acute phase, fluctuating hypersomnia was detected. The MRI (brain) revealed an ischemic lesion in the medial part of the mesencephalon and paramedian thalamus, bilaterally.

*Aims* The aim of the present study is to elucidate the involvement and characteristics of sleep-related breathing abnormalities in the clinical manifestation of the combined paramedian thalamic and mesencephalic stroke.

*Methods* Polysomnographic recordings were accomplished seven times with 1-week interval between the consecutive recordings, toward investigating the early changes of sleep and sleep-related breathing abnormalities.

*Results* Sleep structure examination featured a decrease in N3 and REM ratio and an increase in N1 and N2 ratio with minimal improvement during the recovery period. In contrast, significant changes were found in the breathing pattern: the initial central apnea dominance was followed by obstructive apneas with a gradual decrease of the total pathological respiratory events.

*Conclusion* In addition to the structural abnormality of the sleep regulating network, sleep-disordered breathing is another possible cause of hypersomnia in patients afflicted with the present localization of the lesion.

**Keywords** Paramedian thalamus · Mesencephalon · Stroke · Hypersomnia · Obstructive apnea · Central apnea

# Introduction

Vascular lesion of the bilateral paramedian thalamus is rare, but generally features a well-known syndrome including vertical gaze palsy, amnestic disturbances, and hypersomnia. In some cases, the lesion may also extend to the mesencephalon as well. The anatomical–vascular background of this lesion is the aberrant Percheron artery variation. In such circumstances, the type II variation of paramedian arteries arise from the same side (P1 segment), bifurcate and supply the thalamus bilaterally [1–6]. The mesencephalic lesion is explained due to the thalamic–subthalamic arteries rising together with the mesencephalic branch which supplies the paramedian portion of the midbrain. The clinical course of the disease is fluctuating: mild improvement in hypersomnia and transient worsening period can be observed [3]. In some cases, total recovery of the symptoms was found [7].

The lesion of the abovementioned vascular territory overlaps with the localization of the ascending reticular activating system which may explain the background of the major complain of the patient suffering from hypersomnia.

A series of investigations proved 40 to 70 % of stroke patients suffer from different forms of sleep-disordered breathing [8–10]. Sleep-related breathing disorders (obstructive apnea syndrome, central sleep apnea syndrome, and Cheyne–Stokes breathing) are well-known risk factors for stroke [11,

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12] due to widespread pathophysiological backgrounds (hemodynamic factors, hypoxia, increased blood pressure, formation of reactive oxygen species, inflammatory processes, etc.) [13–15]. In some cases—depending on the localization of stroke—the lesion may serve as anatomical and functional background to develop sleep disordered breathing, which may increase the detrimental effect of original vascular lesion in the patient. Notably, only a small amount of data exhibits the dynamic changes sometimes revealed in the sleep disordered breathing severity following a stroke and after a given measure of time, gradual improvements in the severity of sleep apnea were observed [16].

The brainstem represents a special territory for sleep and breathing regulation [17–20]: the role of lower brainstem (medulla) in the autonomic control of breathing and the consequences seen in the generation of sleep disordered breathing is widely recognized, but there is only sporadic data describing the consequence and dynamic characteristics of the mesencephalic and thalamic lesions on breathing abnormalities.

We examined a patient with bilateral mediodorsal thalamic and upper brainstem (mesencephalic) lesion to detect and follow sleep-related breathing abnormalities and sleep architecture to fully comprehend the background of hypersomnia of the patient with the abovementioned lesions.

#### Methods

A 62-year-old woman was admitted to the neurology department with complaints of impaired consciousness. The patient spent the first 2 days in a comatose state and eventually gained consciousness; however, her unresponsiveness developed into hypersomnia (more than 20 h of sleep per day) which was the primary complaint of the patient during our observation.

Physical neurological examination showed signs of vertical gaze palsy. During the examined period, no significant change was seen in the neurological symptoms indicating a functionally stable condition.

According to the guidelines, all the necessary examinations were done: computer tomography of the head, lab tests, carotid, and vertebral artery ultrasound and cardiologic examination.

An MRI (brain) was performed shortly after admitting the patient and once again, 4 weeks later, in efforts to control possible changes in the lesion.

To examine the sleep–wake cycle and sleep-related respiratory abnormalities, we performed polysomnographic examination relative to the gold standard [21]. Recorded electrode montage covered the EEG channels (C3, C4, F3, F4, O1, O2 position according to the international 10-20 system), eye movement; chin muscle EMG, nasal air flow, thoracic and abdominal breathing effort, ECG, pulse rate, oxygen saturation, limb EMG activity body position sensor and microphone for recording of potential snoring.

Polysomnographic abnormalities and sleep were scored and staged according to the latest guideline of the American Association of Sleep Medicine [21].

The length of one polysomnographic examination was at least 20 h which covered the whole night and significant amount of daytime to visualize the sleep–wake pattern of the patient and to examine the basic characteristics of the sleep period (sleep architecture and the cardiorespiratory events).

Polysomnographic recording was repeated seven times with the interval of 1 week, to follow the changes of sleep architecture and respiratory abnormality during the acute and subacute phase.

#### Results

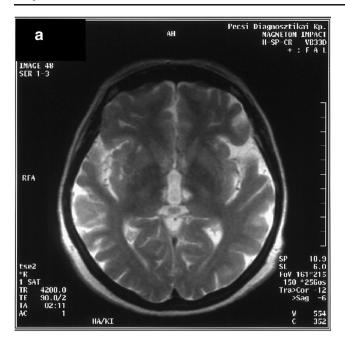
Neurological examination of the patient showed vertical gaze palsy and hypersomnia, which persisted (with a minor degree of fluctuation) during the whole examined period. Other cranial nerve involvement, paresis, reflex asymmetry, signs of pyramidal tract lesion, sensory and coordination abnormalities were not found at the initial phase of the course of the disease nor at the conclusion of examination during hospitalization.

Computer tomography of the head excluded the intracranial bleeding and did not show hypodenz signal alteration in the initial phase or signs of former strokes. Blood chemistry and hemorheologic parameters were in the normal range. Carotid and vertebral ultrasound examination revealed no significant stenosis of the extracranial arteries. Cardiologic screening did not prove the existence of embolic origin of the patient's complains.

MRI showed T2 hyperintense and T1 hypointense lesions from the pontomesencephalic junction through the mesencephalon to the thalamus bilaterally terminated in the mediodorsal nuclei of the thalamus. An MRI was repeated 4 weeks following the onset of the symptoms exhibiting no change of the extent and localization of the lesion. MR angiography showed normal carotid and vertebrobasilar arteries and Willissi circuits. This structural lesion functionally corresponds to the upper part of the reticular formation (Fig. 1).

Polysomnographic examinations were performed to record sleep architecture and sleep-related breathing disturbances seven times within 1 week's time.

During the first examination, all types of sleep-disordered breathing abnormalities were apparent, without any predominance of apnea types (obstructive, mixed, central type), and a high number of hypopneas were found. The indexes for obstructive apneas, central apneas, and mixed apneas are 0.5, 0.1, and 0.2/h, respectively. Hypopnea index was 33.9/h. After 1 week, a substantial change in the breathing pattern was observed: elevation of central apnea index without any



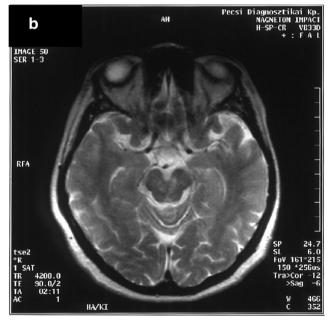


Fig. 1 T2-weighed MR images of the patient shows bilateral vascular lesion of the midbrain and upper brainstem

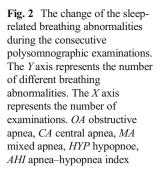
significant change in other types of apneas. At this time, the indexes for obstructive apneas, central apneas, and mixed apneas were 0.3, 15.7, and 2.7/h, respectively. Additionally, the formerly mentioned abnormalities hypopnea index was reduced (15.4/h). The increase of the central apnea number was only a transient event and a rapid decrease was noted during the examination completed 1 week later. During the follow-up examination (1 week later), a mild elevation of apnea was discovered as opposed to the central apneas. Indexes for obstructive apneas, central apneas, and mixed apneas

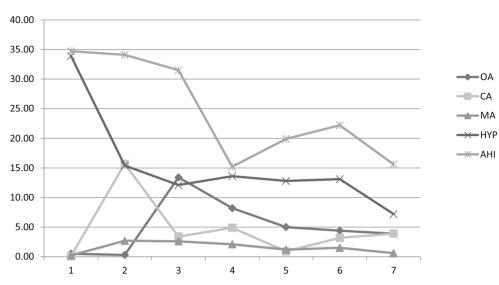
were 13.4, 3.4, and 2.6/h, respectively, and the hypopnea index reduced to 12.1/h during the third polysomnographic recording. In the time following this examination, gradual and a diminished decrease of apnea index and hypopnea index were seen with consequent apnea-hypopnea index change. In a recording made 1 week later, no additional increase of central apnea was notable. Obstructive apnea index was 8.2, 5, and 4.4/h during the fourth, fifth, and sixth recordings, while the central apnea index reduced to 3.2/h with a slight fluctuation until the sixth examination. Decrease of mixed apnea index reached the level of 1.5/h on the sixth recording. Upon the seventh examination, the apnea-hypopnea index was reduced to the one third of its initial value with a dominance of hypopneas. The indexes for obstructive apneas, central apneas, and mixed apneas were 3.9, 3.9, and 0.6/h with a reduction of hypopnea index to 7.2/h.

Figure 2 characterizes the trends of different types of apneas, hypopneas, and apnea–hypopnea index changes during the seven polysomnographic sessions.

During the initial phase of the patient's hospitalization despite the physically coma-like alteration of consciousness, the first polysomnographic examination showed N1 and N2 sleep phase dominance with minimal, but obvious presence of REM phase indicating the signs of regulation instead of the comaspecific changes in the sleep architecture. During serial polysomnographic examinations, a variable increase in the conscious state (improvement of the hypersomnia) was noted. Later sleep patterns were characterized by N2 phasedominance and slight increase of REM phases. N3 and REM ratio diminished (compared with the age specific standards), and N2 ratio increased in the examined periods. The sleep-wake cycle was characterized by the irregular change of the awake state and sleep with variable lengths of awake period with one main sleep period during the night. These findings indicated the instability of sleep-wake cycle regulation. The series of polysomnographic examination describe mild improvement of changes of sleep architecture and sleep-wake cycle parameters comparing the first and former examinations. The sleep phase and stage distribution are summarized in Table 1.

Evaluation of the data, following initial and transient elevation of central apnea count, a mild increase followed by gradual and slow decrease of obstructive apnea index was seen. Gradual decrease of hypopnea count was detected from the first to the last examinations. The apneahypopnea index decreased continuously from the acute phase to the end of the examination period. The sleep phase and sleep–wake cycle pattern showed instability of the regulation (fragmented sleep–wake pattern) and superficial sleep (N2) dominance with the signs of active regulation (preserved REM phases, periodic alteration of the non-REM and REM phases) and mild improvement of the hypersomnia of the patient.





### Change of the OA, CA, MA, HYP and AHI

# Discussion

The major symptoms of the patient were vertical gaze palsy and hypersomnia as a consequence of bilateral lesions of paramedian thalamus and mesencephalon caused very likely by ischemic stroke. Reticular formation plays a substantial role in the sleep–wake regulation [18]. The lesions responsible for the symptoms mentioned above overlaps with the upper part and termination area of reticular formation (mesencephalon and paramedian thalamus bilaterally) explaining the observed hypersomnia.

Meta-analysis of 29 articles with more than 2000 stroke patients showed lack of association of stroke type and type of breathing abnormality [22]. The examinations displayed obstructive apnea dominance over the central apnea (7 %) in patients with stroke. The frequency of sleep-disordered breathing was higher in the case of infratentorial stroke than in

 Table 1
 Characteristic parameters of the sleep architecture during the seven consecutive polysomnographic examinations

Examination	TST	N1	N2	N3	REM
1	1159.00	35.90	49.50	11.20	3.40
2	1116.00	33.50	55.20	5.70	5.60
3	995.00	35.20	53.30	7.20	4.30
4	987.00	40.00	48.70	4.20	7.10
5	993.00	20.10	59.30	12.30	8.30
6	1139.00	29.30	51.20	11.60	7.90
7	872.00	26.40	52.10	14.40	7.10

Examination: number of polysomnographic examination; values: length of the TST, N1, N2, N3, and REM in minutes

TST total sleep time, N1, N2, N3 nonrapid eye movement phases (according to the AASM scoring manual), REM rapid eye movement supratentorial type. According to Bassetti's examination [23], sleep-disordered breathing rarely has localizing value. In hemispheric stroke (for example in middle carotid artery territory, mainly in bilateral cases), the Cheyne–Stokes breathing is the primary characteristic [24].

Former observations emphasized the role of brainstem in pathogenesis of sleep-disordered breathing [9, 17, 25].

Stroke can disrupt breathing in several ways: structural alteration of the respiratory neurons in the brainstem, functional or neurochemical alteration of the respiratory neurons, involvement of the voluntary control during wakefulness, and failure of the afferent regulation and descending control pathways of the respiratory neurons [26].

The majority of these case studies are primarily based upon single polygraphic or polysomnographic recordings, which are insufficient to demonstrate the dynamic changes of events during the acute, subacute, and chronic phases.

The strategic objective of this study was to perform a longitudinal examination of sleep-disordered breathing pattern changes due to the lesion of bilateral thalamus and mesencephalon lesions corresponding to reticular formation.

Our serial polysomnographic examinations proved the increase of sleep time, and the presence of active regulation of sleep with the decreasement of N3, increased N1 and N2 ratio and decreased, but preserved REM.

The serial polysomnographic examination reveals characteristic trends in the distribution of different types of breathing abnormalities: initial central apnea dominance turned into obstructive apnea with a decrease of apnea–hypopnea index.

Our former examination of a patient with brainstem stroke (bilateral mesencephalic laesion) showed central apneas and periodic breathing, which underlines the role of mesencephalon in the pathogenesis of central apneas (Faludi, unpublished data). In the present examination, in contrast with the mesencephalic lesion, the central apnea dominance was only a transitoric phenomenon. It can be explained with the extension and functional heterogenity of the lesion [4].

In the present case, the observed breathing pattern abnormality supposed to be the consequence of the combination of brainstem involvement and impairment of the descending respiratory pathways. The dynamical aspect of the breathing abnormality can be explained by the mild change of the extent of the lesion affecting the descending control pathways. In majority of cases, the observed breathing abnormality cannot be explained by the lesion [23]. A minor neurological deficit can cause severe sleep-disordered breathing without strict association of the pattern and localization. The association of the localization of stroke and type of breathing abnormality is high in case of medullary infarct only.

Different forms of sleep-disordered breathing can cause microarousals affecting sleep architecture, causing sleep fragmentation and a decrease in the amount of deep sleep amount. The consequence is the excessive daytime drows-iness which is a characteristic symptom of bilateral paramedian thalamic lesion. The significance of this pathophysiological route that—beside classical brain stem origin—the sleep-disordered breathing contributes to the hypersomnia and can be treated by continuous positive airway (CPAP) therapy [27–29].

The significant finding of our examination is the dynamic change of the sleep-disordered breathing in the acute and subacute phase of lesion affecting the paramedian thalamus and mesencephalon bilaterally. According to previous studies, our examination showed a gradual decrease of apnea–hypopnea index during the course of the disease, but it is the first study which effectively demonstrates change in types of apneas in acute and subacute phase after the onset of lesion.

Despite the improvement of the sleep-disordered breathing, we did not find substantial improvement in the patient's hypersomnia. There may be several explanations of these phenomena. First, the localization of the vascular lesion overlaps upper part of the reticular formation which on its own can explain the remaining hypersomnia [18, 30]. In addition, it is regularly observed that the remaining degree of sleepdisordered breathing alone is able to cause excessive daytime somnolence in an otherwise healthy subject [31].

Examination and therapeutic intervention of the sleepdisordered breathing with effective CPAP or BiPAP therapy in the acute phase may reduce the risk of extending of the vascular lesion with the possible chance of better functional outcome.

In contrast to the tendency of restoration of breathing pattern, the neurological symptomatology showed no major recovery. This fact underlines the importance of sleep examination (polygraphic or polysomnographic) to possibly understand other axis of pathology which—in turn—can decrease the functional outcome of the patient.

The common link of the stroke and sleep disordered breathing is the ischemic penumbra which has the potential reversibility provided by the reestablishment of the local blood flow [32]. After a few minutes of ischemia, complete damage of the core can be found. During the subacute phase, the irreversible damage can expand to the penumbra by several mechanisms. In this process, the hypoxia and lactacidosis plays a pivotal role. Further ischemic process (within 6-8 h) will affect the penumbra, converting it into irreversible infarct. Experimental data concerning the relationship of ischemic penumbra and sleep apneas are desirable. The different forms of sleep-disordered breathing abnormalities can affect the perfusion by the continuous oscillation of the hemodynamic parameters and by repetitive hypoxic process leading to free radical formation and lactacidosis. The change of the extent of the ischemic lesion can affect the breathing regulatory networks.

The essence of a present investigation may emphasize the importance of sleep examinations and proper treatment of sleepdisordered breathing in the primary and secondary preventions of a potential stroke. As it was mentioned by several studies [27–29], in addition to the routine therapeutic procedures, examination and treatment of sleep-disordered breathing (by preventing the repetitive desaturations and its consequences) in the acute and subacute phase of stroke may be helpful to reduce the damage of ischemic penumbra and provide better functional outcome of the patient.

**Conflict of interest** The authors reported no financial disclosure and conflict of interest.

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