Joubert Syndrome and Biot’s Respiration Misdiagnosed as Epilepsy

Joubert Syndrome (JS) is a rare ciliopathy characterized by neurodevelopmental delay and irregular breathing patterns. Here we present a patient with JS, who was misdiagnosed as having epilepsy. A five-year-old girl with JS was referred due to excessive daytime sleepiness. She was diagnosed as having apneic seizures, and given antiseizure medications with no benefit. Apneas were present during wakefulness lasting for more than one minute, with sudden myoclonic jerks characterized by the extension of the body and the flexion of the limbs at the resume of respiration with paradoxical breathing, hyperpnea separated by apneas ends with a sudden myoclonic jerk characterized by the extension of the body and the flexion of the limbs at the resume of the respiration. The patient was effectively treated by adaptive servo ventilation therapy.

Joubert syndrome (JS) is a rare ciliopathy characterized by hypotonia, ataxia, psychomotor delay and irregular breathing patterns. The disease is genetically heterogeneous with more than 35 genes currently known to cause it when mutated. The pathognomonic feature of JS is a distinctive cerebellar and brainstem malformation on axial cranial magnetic resonance imaging (MRI) known as the “Molar Tooth Sign” (MTS) (Figure 1).

JS may be accompanied by the additional systemic involvements, and classified as follows: Pure JS (classical form), JS with ocular defect (JS-O), JS with renal defect (JS-R), JS with ocurolrenal defects (JS-OR), JS with hepatic defect (JS-H), JS with orofaciiodigital defects (JS-OFD). Although the epileptic seizures are not common in JS, an approximate prevalence of 10% was reported in a case series. Sleep-related problems are frequently over-

**Keywords:** Joubert Syndrome 2; respiratory disorders; sleep apnea syndromes

**Anahat Kelimeler:** Joubert sendromu 2; solunum hastalıkları; uyku apne sendromları

**REFERENCE MATERIAL:**


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**For the video of the article:**

**VIDEO 1:** The paradoxical breathing and hyperventilation separated by apneas ends with a sudden myoclonic jerk characterized by the extension of the body and the flexion of the limbs at the resume of the respiration.

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**Correspondence:** Başak YILMAZ,
Department of Neurology, Division of Clinical Neurophysiology, Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Istanbul, Türkiye

**E-mail:** basakyilmaz987@gmail.com

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looked in these patients, although almost all patients with JS report at least one sleep-related complaint on through questioning.7 Sleep apnea, tachypnea, or irregular breathing both in wakefulness and during sleep are not uncommon. In this context, we here present a patient with JS-R, who was misdiagnosed as having epilepsy due to myoclonus-like jerks associated with the Biot’s respiration.

**CASE REPORT**

A five-year-old girl with JS was referred to our sleep center due to excessive daytime sleepiness (EDS) and fatigue. She was born with a weight of 3,920 g at 38+5 weeks of gestation with C/S due to hydrocephalus. The head circumference was 38 cm, and she was 53 cm in height. The Apgar score was 1.5 points because of the two long-lasting apnea episodes for which she was internalized in the intensive care unit for three days. She had the diagnosis of JS, with the typical findings compatible with JS in physical examination and the cranial MRI features showing cerebellar vermis hypoplasia and the MTS (Figure 1). The electroencephalography (EEG) was normal. With the pre-diagnosis of apneic seizures, she was given phenobarbital. Because no apneic episodes were noticed during the follow-up period, the patient was externalized. In family history, there was no consanguinity between the parents. Genetic testing demonstrated a mutation in *ARL13B* gene.

At the age of one year, the apneic episodes have re-emerged; the dose of phenobarbital was increased with no benefit, and no improvement was obtained with different anti-seizure medications. Pulse oximeter, aspirator, oxygen tube and concentrator were provided for the house care, and she was given regular physiotherapy sessions. Bilateral renal parenchymal disease was noticed at the age of four, and the patient was diagnosed as having JS-R. In her latest examination, she had no speech, was barely able to sit without support, and walk only with bilateral support.

On her admission to our Sleep and Disorders Unit, we noticed that she had attacks of apnea semi-continuously during wakefulness lasting for more than one minute. The apneic attacks ended with a sudden myoclonic jerk characterized by extension of the body and flexion of the limbs at the resume of the respiration with paradoxical breathing, hyperventilation and tachypnea (Video 1). A full-night polysomnography (PSG) was performed and evaluated according to the international guidelines for children.8 The International Classification of Sleep Disorders was used in the diagnosis of the sleep-related disorders.9

PSG parameters of the patient are given in Table 1. The patient was diagnosed with obstructive sleep apnea syndrome (OSAS) and central sleep apnea syndrome (CSAS).

<table>
<thead>
<tr>
<th>TABLE 1: PSG parameters of the patient.</th>
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<tbody>
<tr>
<td><strong>PSG data</strong></td>
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<tr>
<td>Total recording time (minutes)</td>
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<tr>
<td>Total sleep time (minutes)</td>
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<tr>
<td>Sleep latency (minutes)</td>
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<td>REM sleep latency (minutes)</td>
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<td>Sleep efficiency (%)</td>
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<td>N1 sleep (%)</td>
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<td>N2 sleep (%)</td>
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<tr>
<td>N3 sleep (%)</td>
</tr>
<tr>
<td>REM sleep (%)</td>
</tr>
<tr>
<td>AHI for the obstructive events (hour)</td>
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<tr>
<td>AHI for the central events (hour)</td>
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<td>Minimum oxygen saturation (%)</td>
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PSG: Polysomnography; REM: Rapid eye movements; AHI: Apnea-hypopnea index.
Biot’s respiration was present semi-continuously during wakefulness and sleep (Figure 2). The majority of the abnormal respiratory events were associated with sudden, myoclonic jerks occurring at the end of the apneic periods. No epileptic features or epileptiform discharges were observed during these attacks. In the management of the patient, the non-invasive mechanical ventilation (NIMV) treatment with positive airway pressure (PAP) was planned. Continuous PAP or bi-level PAP with S/T mode failed to control obstructive and central types of events. The adaptive servo ventilation (ASV) therapy resulted an effective control for all types of abnormal respiratory events (at a minimum expiratory pressure of 4 cmH₂O, maximum expiratory pressure of 13 cmH₂O, pressure support between 3-10 cmH₂O, maximum inspiratory pressure of 20 cmH₂O, and respiratory rate of 21/minutes) (Figure 3). With the normalization of the respiration under ASV therapy, myoclonic jerks also disappeared, and the anti-seizure medications were quitted. The parents were advised to use ASV therapy all through the night during sleep, and for 10 to 20 minutes at every two hours during the daytime.

A written informed consent was obtained from the parents of the patient for this publication.

DISCUSSION

The abnormal respiratory control is thought to result from the brainstem involvement in JS, which affects

![Figure 2: Polysomnography recordings show the Biot’s respiration during wakefulness (a), and sleep (b).](image-url)
the interaction of respiratory oscillators in the brainstem. Although these apneic events are well-known in JS, congenital alveolar hypoventilation syndrome due to PHOX2B gene mutation, or neuromuscular diseases with respiratory dysfunction, as congenital myasthenic syndromes should also be considered in the differential diagnosis of apneas in newborns. On the other side, different movements and behaviors may also complicate apneic spells, especially in the newborns and the children, which endangers the diagnosis. As in our patient, apneic episodes associated with myoclonic jerks may be misinterpreted as epileptic phenomena. Although EEG may be helpful in the diagnosis of apneic events to be epileptic in origin, attacks of cardiac origin such as asystole, or the presence of respiratory dysfunction requires polygraphic recordings.

There are only case reports in the literature, describing patients with JS and sleep-disordered breathing. The clinical symptomatology of sleep-disordered breathing may be subtle varying from snoring, EDS to sudden infant death syndrome, requiring a detailed questioning. The early detection and the management of the respiratory problems in JS is emergent, as the treatment may have a beneficial impact on the course and the prognosis of the disease. In the presented case, Biot’s respiration during wakefulness and sleep, pediatric OSAS and CSAS were associated with JS. Because of the associated abnormal movements characterized by myoclonic jerks, the patient was misdiagnosed as epilepsy, which caused a delay in the diagnosis and the treatment of sleep-disordered breathing. To the best of our knowledge, there is no similar case report in the literature regarding a patient with JS and myoclonic jerks related to the abnormal respiratory patterns, though obstructive or central type of apneas are known to trigger non-epileptic spells. A similar case series were reported in patients with Rett syndrome, where paroxysmal episodes of hyperventilation and apnea during wakefulness were misdiagnosed as epileptic phenomena until they were diagnosed to be non-epileptic spells by video-polygraphic recordings.

The gold standard treatment of the sleep-disordered breathing is the NIMV. Night-time oxygen therapy and bi-level PAP in S/T mode were reported to be effective in the treatment of central apneas in JS, though the presence of both obstructive and central types of events or irregular breathing patterns may complicate the treatment, requiring flow or volume monitoring devices. In our patient, the treatment with ASV mode of PAP therapy was needed, which effectively controlled all types of abnormal respiratory patterns. Although the daytime respiratory problems are better known in JS, sleep-related breathing disorders should also be questioned in detail in these children, and the polysomnographic recordings should be performed in the presence of clinical suspicion.
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No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions
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