Sleep-related breathing disorders associated with the characteristics of underlying congenital rare diseases of Moebius syndrome and Poland syndrome

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Keywords
Moebius syndrome, obstructive sleep apnoea, Poland syndrome, sleep-related breathing disorders, sleep-related hypoventilation disorders.

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Received: 3 February 2020; Revised: 14 April 2020; Accepted: 21 April 2020; Associate Editor: Daniel Ng.

Respirology Case Reports, 8 (5), 2020, e00579
doi: 10.1002/rcr2.579

Abstract
A 24-year-old woman was referred to us with daytime sleepiness. She has two congenital intractable and rare diseases, namely, Moebius syndrome and Poland syndrome. Physiological examinations and a detailed usage analysis under a ventilation device helped to conclude that hypoglossal nerve paralysis and thoracic deformity from her two underlying diseases were associated closely with her final diagnosis of obstructive sleep apnoea and sleep-related hypoventilation due to medical disorders. Bilevel positive pressure ventilation with auto-titrating expiratory positive airway pressure was effective. This is the first report that describes in detail the causal interactions between underlying two intractable and rare diseases and sleep-related breathing disorders.

Introduction
Obstructive sleep apnoea (OSA) is a common disorder characterized by episodic obstruction to breathing due to upper airway collapse during sleep resulting in intermittent hypoxia, hypercapnia, and nocturnal awakening. Phenotypic traits that contributed to the pathogenesis of OSA have recently been reported. These include anatomical (narrow/collapsible upper airway) and non-anatomical traits including reduced pharyngeal dilator muscle activity [1]. Congenital intractable and rare diseases could induce the development of sleep-related breathing disorders (SBDs) such as OSA through the physical conditions associated with underlying these diseases [2]. Here, we report an adult SBD patient whose various physiological examinations demonstrated unique relationship between her congenital intractable and rare diseases and SBDs.

Case Report
A 24-year-old woman with a history Moebius syndrome and Poland syndrome was referred to us from former sleep clinic. When she was 5 years old, an anaesthesiologist spotted her temporary cessation of breathing under intravenous general anaesthesia, but further detailed examination has not been performed. In her former clinic, she was diagnosed with severe OSA by overnight polysomnography (PSG) (Table 1) and was treated with continuous positive airway pressure (CPAP). However, applying automatic pressure regulation (lower/upper limit pressure 4/18 cmH2O) failed not only to normalize her residual hypopnoea events with average apnoea–hypopnoea index (AHI) of 10.3 events per hour on CPAP by evaluating log data, but also to improve her subjective sleepiness. She was then referred to our hospital. In her first physical examination, obese with a body mass index (BMI) of 45 kg/m², strabismus, tongue deviation...
towards the right side due to right hyoglossus nerve paralysis (Fig. 1A), deficit in her left fingers, and left side hypoplasia of her chest (Fig. 1B) were observed. Her axial computed tomography scans of the chest mediastinal window showed an obvious laterality in her lung field, rib cages, and muscles in the thorax (Fig. 1C). Physiological examinations such as arterial blood gas analysis, spirometry, and respiratory muscle strength test showed hypercapnia, restrictive pulmonary dysfunction, and lower respiratory muscle strength on supine and right-side recumbent positions, respectively (Table 1). We conducted her second overnight PSG with simultaneous transcutaneous carbon dioxide pressure (PtCO2) monitoring (Table 2). The PSG result scored by American Academy of Sleep Medicine (AASM) Version 2.4 met the criteria of SBDs which was further classified into OSA and sleep-related hypoventilation according to the International Classification of Sleep Disorders (ICSD-3). Interestingly, she also showed good reproducible laterality of OSA severity, which is discussed in detail later. We treated her with non-invasive positive pressure ventilation (NPPV) equipped with an auto-titrating expiratory positive airway pressure (EPAP) mode during sleep with auto-bilevel and bi-flex mode (lower limit EPAP at 4 cmH2O, lower/upper limit pressure support at 2/8 cmH2O, and maximum inspiratory limit pressure at 20 cmH2O) which she tolerated very well. The NPPV usage analysis by evaluating device log data showed a normalized residual AHI. Her daytime sleepiness disappeared and her partial pressure of carbon dioxide (PaCO2) when awake also normalized. Written informed consent was obtained from the patient for this case report.

### Discussion

We herein report a case of newly diagnosed SBDs (severe OSA and sleep-related hypoventilation) associated with

| Table 1  | Physiological examinations. |
|----------|----------------------------|
| **Arterial blood gas** |                  |
| pH       | 7.435                      |
| PaCO2 (mmHg) | 45.0                        |
| PaO2 (mmHg) | 77.8                        |
| HCO3− (mmol/L) | 29.5                      |
| A−aDO2 (mmHg) | 15.9                      |

| **Spirometry** | Value      | % Predicted |
|----------------|------------|-------------|
| VC             | 2.18 L     | 70%         |
| FEV1           | 1.72 L     | 63.4%       |
| FEV1/FVC       | 80.4%      |             |

| **Respiratory muscle strength test** | Supine (% predicted) | Right side recumbent (% predicted) | Left side recumbent (% predicted) |
|-------------------------------------|----------------------|------------------------------------|-----------------------------------|
| Max. inspiration                    | 72.5%                | 86.3%                              | 113.1%                            |
| Max. expiration                     | 101.5%               | 67.9%                              | 74.5%                             |

A−aDO2, Alveolar-arterial Difference in oxygen; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; Max., maximum; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; VC, vital capacity.

Figure 1. Images of the patient taken at admission. Patient’s face showing tongue deviation towards the right side (A). Patient’s chest showing obvious laterality of the breast (B). Computerized axial tomography scan of the chest mediastinal window showing complete loss of the left major and minor pectoralis muscles (long arrowhead), hypoplasia of the left intercostal muscle (short arrowhead), dysplasia of the left rib (long arrow), and poor fusion of the left rib and sternum (short arrow) with a small left thorax (C).
her congenital intractable and rare diseases of Moebius syndrome and Poland syndrome. Moebius syndrome is a rare disease that causes hypoplasia or deficiency of the cranial nerve nucleus associated with prenatal ischaemia of the brain stem [3]. Our case not only had facial nerve paralysis and abnormal limb morphology, but also hypoglossal nerve paralysis which is involved in 25% of Moebius syndrome cases [4]. Hypoglossal nerve paralysis causes a reduction of pharyngeal dilator muscle activity [5]. In fact, an animal model of OSA induced by hypoglossal nerve paralysis has been established [6]. Therefore, in terms of the phenotypic trait for her OSA, her non-anatomical ineffective or reduced pharyngeal dilator muscle activity was also suggested to contribute synergistically to her anatomical factor.

In terms of anatomical trait, her severe obesity itself was strongly suggested to be the main causative factor contributing to her OSA. Nevertheless, the AHI was higher; in other words, worse OSA severity in right-side recumbent position compared to other positions with good reproducibility of her twice-performed PSG results supports the idea that her tongue deviation towards the affected side could also be a factor to induce her OSA by causing narrower airway.

A diagnosis of Poland syndrome is based on the characteristic physical findings of the condition including unilateral pectoral muscle defects, finger defects, rib cage deformities, and diaphragm defects [7]. In our case, all these findings were observed. Similar to our case, 15% of Moebius syndrome cases are accompanied by Poland syndrome in Japan [8]. Hypoplastic pectoral muscle due to Poland syndrome causes a restrictive pulmonary dysfunction at spirometry [9] resulting in hypoventilation. Our case also showed daytime and nocturnal hypoventilation with restrictive pulmonary dysfunction at spirometry (Table 1). The laterality differences of her respiratory muscle strength may be explained by the unilateral hypoplasia and deformities of her chest. Considering her underlying Poland syndrome and all the obese subjects not always producing restrictive pulmonary dysfunction or SBDs, we finally diagnosed her with SBD which was further classified into OSA and sleep-related hypoventilation due to a medical disorder rather than an obesity hypoventilation.

### Table 2 PSG parameters.

|                      | First (26 September 2018) | Second (16 February 2019) |
|----------------------|---------------------------|---------------------------|
| AHI (times/h)        | 78.5                      | 137.8                     |
| Supine AHI (times/h) | 125.1                     | 142.8                     |
| Right lateral AHI (times/h) | 107.8                 | 122.9                     |
| Left lateral AHI (times/h) | 54.0                   | 90.7                      |
| Nadir SpO2 (%)       | 37                        | 38                        |
| 3% ODI (times/h)     | 105.0                     | 154.1                     |
| PtCO2 (average) (mmHg) | NA                      | 55                        |
| PtCO2 >55 Torr (%)   | NA                        | 84.5                      |

AHI, apnoea–hypopnoea index; ODI, oxygen desaturation index; PSG, polysomnography; PtCO2, transcutaneous carbon dioxide pressure; PtCO2 >55 Torr (%), time when transcutaneous carbon dioxide exceeded 55 Torr for total sleep time; SpO2, peripheral capillary oxygen saturation.

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**Figure 2.** Summary of the relationship interactions between the respective underlying congenital interactable rare diseases and sleep-related breathing disorders.
syndrome according to the ICSD-3. The disease interactions between her SBDs and underlying diseases are summarized in Figure 2. Various physiological examinations make it possible to assess the interactions between the patient’s underlying disease, such as the congenital intractable diseases and SBDs. Furthermore, appropriate treatment may contribute to improving SBDs among other patients with congenital intractable and rare diseases.

Disclosure Statement
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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