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Short communication

Chemosensitivity recovery in Ondine's curse syndrome under treatment with desogestrel

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ABSTRACT

Congenital central hypoventilation syndrome (CCHS), or Ondine's curse syndrome, is a rare genetic disorder associated with mutations of the PHOX2B gene. It is characterized by sleep-related life-threatening hypoventilation that requires mechanical ventilation. The ventilatory response to hypercapnia and hypoxia is absent or dramatically reduced. Spontaneous or pharmacologically induced recovery has never been reported.

We have fortuitously observed a case of CO_2-chemosensitivity recovery in a woman with CCHS who took a progestin contraceptive – desogestrel. We hypothesized that the desogestrel could be responsible for this effect. We tested this hypothesis in a second adult patient. Her lack of CO_2-chemosensitivity was documented 5 months before she was prescribed desogestrel. Three weeks after initiation of the treatment she exhibited a ventilatory and sensory response to hypercapnia. This response persisted 3 weeks later.

This is the first documented case of pharmacologically restored chemosensitivity in CCHS. It suggests that a very potent progestin such as desogestrel could unveil latent chemosensitive neural circuits.

1. Introduction

Congenital central hypoventilation syndrome (CCHS), or Ondine's curse syndrome, is a rare genetic disorder associated with various mutations of the homeobox gene PHOX2B (Amiel et al., 2003). It is characterized by sleep-related life-threatening central hypoventilation. Patients with CCHS therefore depend on mechanical ventilation (or diaphragm pacing) at night and during naps, all their life. Diurnal hypoventilation can exist in severe forms. The ventilatory response to hypercapnia and hypoxia is absent or dramatically reduced (Trang et al., 2005). The patients are thus devoid of the interoceptive alarms that normally trigger awakening in the case of life-threatening hypoxia during sleep. Mild or fluctuating phenotypes can lead to tardive diagnosis (Doherty et al., 2007) but there are no known cases of spontaneous or pharmacologically induced recovery.

Progestins could theoretically form a therapeutic avenue since they stimulate ventilation and enhance chemosensitivity in healthy subjects (Bayliss and Millhorn, 1992; Pena and Garcia, 2006) and in some patients with low chemosensitivity (Milerad et al., 1985). However, hypoventilation does not improve during pregnancy in patients with CCHS (Sritippayawan et al., 2002), in spite of the corresponding increase in progesterone.

In this context, we had the surprise to observe an obvious increase in ventilation during exposure to CO_2 in a woman with CCHS previously known to lack any ventilatory response to hypercapnia and who was participating in a research protocol. Systematic questioning uncovered that the patient had been prescribed desogestrel on a daily basis for contraceptive purposes. Because of the known potency of desogestrel (Wiegratz and Kuhl, 2004), we hypothesized that there could be a link between this prescription and the recovery of chemosensitivity. We were then fortuitously presented with the opportunity to formally test this hypothesis in another patient. These two cases are described below. This could

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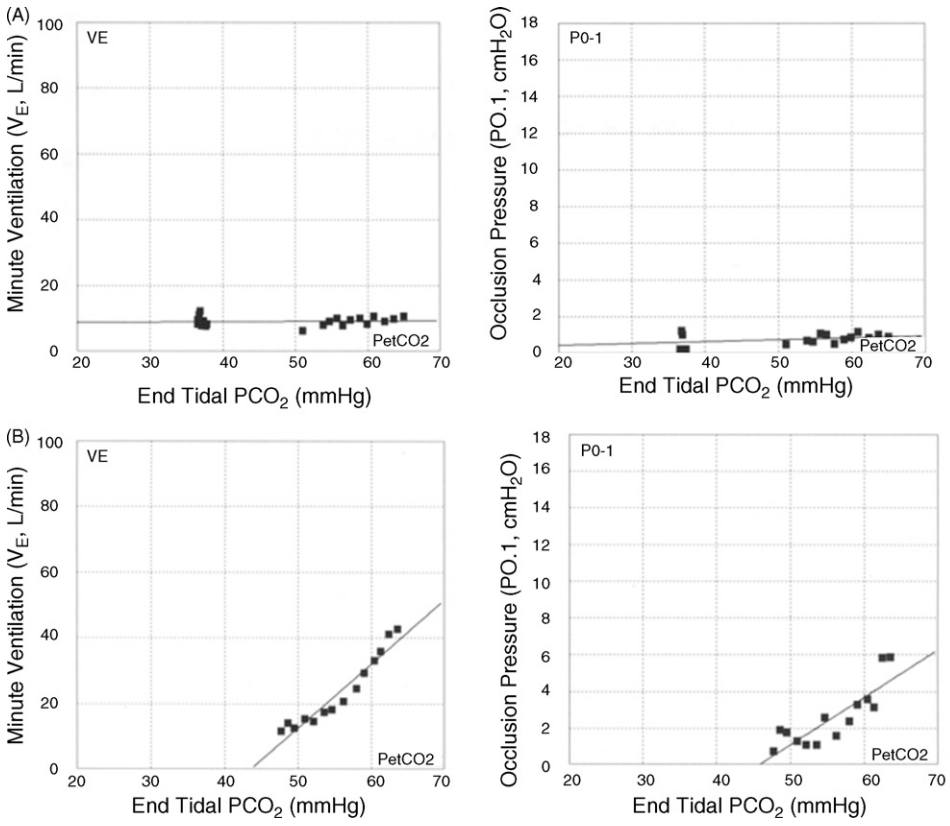

Fig. 1. Ventilatory responses of the first patient during CO_2 rebreathing. Panel A shows the ventilatory response as assessed in 2006. Panel B shows the same assessment in 2009, after about 18 months under desogestrel. In each panel, the left graph shows the changes in ventilation ($\dot{V}_E$) with the increase in end tidal CO_2 partial pressure. The right graph depicts the changes in occlusion pressure ($P_{0.1}$).

represent an important pathophysiological and therapeutic breakthrough in this orphan disease.

2. Methods

The ventilatory response to hypercapnia was assessed using the rebreathing method (Read, 1967). Briefly, the patients breathed through a pneumotachometer in a closed one-way circuit containing a bag filled with a gas mixture of 7% CO_2–93% O_2 (Hyp'Air Compact+, Medisoft, Sorinnes-Dinant, Belgium). We recorded tidal volume (VT), respiratory frequency, minute ventilation ($\dot{V}_E$), and end tidal carbon dioxide partial pressure (PET_{CO_2}). Repeated measurements of the 100 ms mouth occlusion pressure ($P_{0.1}$ – an index of the respiratory neural drive) were obtained through occlusions of the inspiratory limb of the breathing circuit during expiration, that were performed randomly and unbeknown to the patients (Whitelaw et al., 1976).

3. Results

The results were obtained in two patients from the French cohort of CCHS patients (Trang et al., 2005) who are followed on a regular basis by the adult branch of the French reference Center for Ondine syndrome. They gave written consent to the use of the present data for scientific publication purposes.

3.1. First patient: hypothesis generation

The first patient is a 19-year-old woman carrying the 5 alanine expansion mutation of the PHOX2B gene. She was intubated and mechanically ventilated 15 days after birth for severe hypoventilation (pH = 6.87, $Pa_{CO_2} = 170$ mmHg under oxygen therapy) and tracheotomized when 3 months old. She has since been fully dependent on mechanical ventilation during sleep, but she does not exhibit hypoventilation during wakefulness. Her tracheotomy was closed at age 17 in favour of non-invasive ventilation through a nasal mask.

The patient attended the adult branch of the reference center for the first time in 2006. A complete absence of ventilatory response to hypercapnia was documented using the rebreathing method (Fig. 1A). In March 2009, the patient participated in a research protocol, with the usual legal and ethical clearances (Comité de Protection des Personnes Pitié-Salpêtrière, Paris, France). The protocol involved an assessment of the ventilatory response to steady-state hypercapnia. The participants had to breathe through a one-way valve in an open circuit, of which the inspiratory arm was connected to a bag containing a 7% CO_2–93% O_2 gas mixture. To the astonishment of the investigators, the patient exhibited a visible, 2–3-fold increase in $\dot{V}_E$ when exposed to this gas mixture. For confirmatory purposes, the ventilatory response to hypercapnia was assessed 2 days later with the rebreathing method. The baseline PET_{CO_2} was ~ 34 mmHg with a $\dot{V}_E$ of ~11 L/min. $\dot{V}_E$ started to increase at a threshold PET_{CO_2} just below 50 mmHg and the slope of the response was 1.95 L/min/mmHg, within the normal range (Fig. 1B). The rise of $\dot{V}_E$ resulted from an increase in respiratory frequency (~16/min to ~27/min) an in V_T (~0.7–1.5 L). $P_{0.1}$ also increased, from ~1 cm H_2O to ~5–6 cm H_2O.

In answer to extensive questioning, the patient told us that she had been prescribed desogestrel 75 μg daily for contraception, about a year and a half before. Because of the known potency of desogestrel as a progesterone agonist (Wiegratz and Kuhl, 2004) we assumed a putative link between this drug and the recovery of the ventilatory response to hypercapnia.

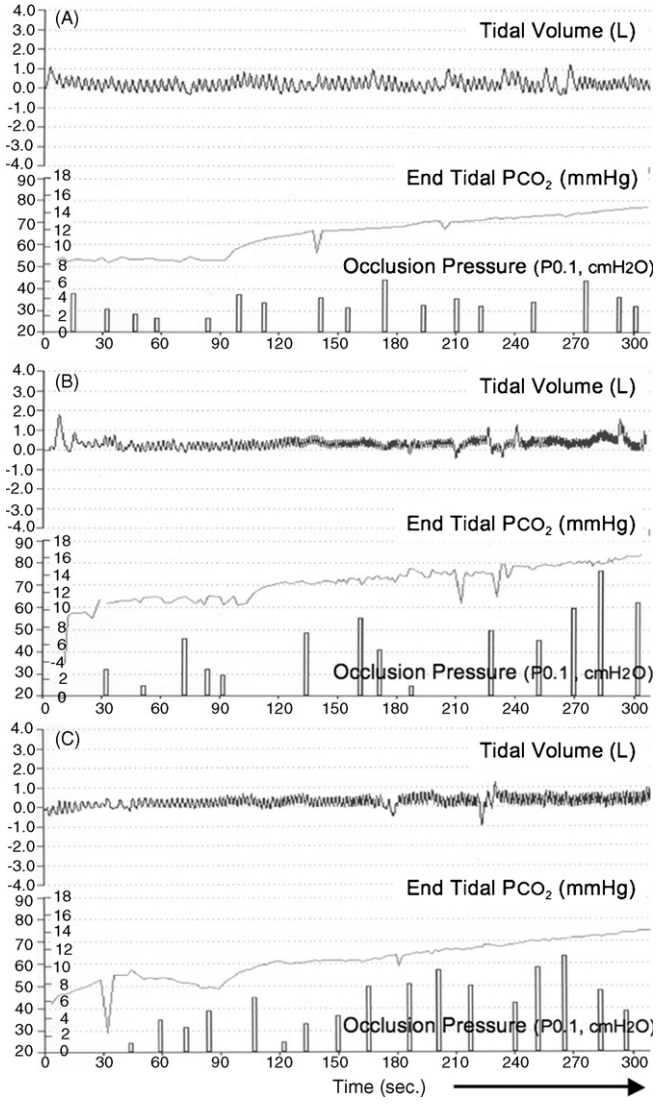

Fig. 2. Ventilatory responses of the second patient during CO_2 rebreathing. Each panel shows the tidal volume (top tracing), the end tidal P_{CO_2} (middle tracing) and the occlusion pressure ($P_{0.1}$; vertical bars) over time. Panel A: recording performed in July 2009, before the treatment with desogestrel. There is no ventilatory or $P_{0.1}$ response whatsoever. Panel B: recording performed 19 days after beginning the treatment with desogestrel. Respiratory frequency increases above a PET_{CO_2} of circa 70 mmHg, with a marked increase in $P_{0.1}$. Panel C: recording performed 40 days after beginning the treatment with desogestrel, again with a marked rise in breathing frequency and $P_{0.1}$ above a PET_{CO_2} of approximately 60 mmHg.

3.2. Second patient: hypothesis testing

The second patient is a 30-year-old woman carrying the 6 alanine expansion mutation of the PHOX2B gene. She was intubated and mechanically ventilated at birth and trachetomized when 5 months old. She has since been fully dependent on mechanical ventilation during sleep. In contrast with the first patient, she exhibits hypoventilation during wakefulness (Pa_{O_2} ~75 mmHg; Pa_{CO_2} ~55 mmHg). The complete absence of ventilatory and sensory responses to hypercapnia was documented several times – and no later than July 2009 (Fig. 2A) – using the rebreathing method.

In December 2009, the patient asked her gynecologist for oral contraception. Fortuitously, the contraceptive pill chosen was desogestrel 75 μg daily, as in the first patient. In view of the above hypothesis, we proposed to the patient, who had accepted to participate in the same protocol as the first one, to assess her ventilatory response to hypercapnia after the initiation of treatment. She therefore underwent a new rebreathing test 3 weeks after the beginning of the treatment. She breathed in the circuit through her tracheotomy cannula (7 mm ID). Her baseline PET_{CO_2} was 62 mmHg with a $\dot{V}_E$ of ~10 L/min. $\dot{V}_E$ started to increase at a threshold PET_{CO_2} of 70 mmHg, to reach 27 L/min at a PET_{CO_2} of 84 mmHg. The slope of the response was 1.13 L/min/mmHg, within the normal range. The rise of $\dot{V}_E$ resulted from an increase in respiratory frequency (~25/min to ~60/min) whereas VT remained stable (~0.4 to 0.5 L) (Fig. 2B). $P_{0.1}$ also increased, from ~3–6 cm H_2O to ~11–14 cm H_2O (Fig. 2B). The patient reported respiratory sensations and a marked anxiety that she had never experienced previously in similar circumstances. Repeated testing 3 weeks later showed a persistent ventilatory response to CO_2 (slope 0.53 L/min/mmHg; threshold ~60 mmHg) (Fig. 2C), still accompanied by respiratory sensations ("I feel the need to breathe", sic).

Of note, the resistance of the tracheotomy cannula may explain why the response of this patient was characterized by an increase in frequency only (as compared with the more typical response exhibited by the first patient, namely a combined increase in V_T and respiratory frequency).

4. Discussion

Observing a response to carbon dioxide in patients notorious for complete unresponsiveness to such stimulation since birth came as a shock to the physicians and to the patients themselves. Because of the clear cut and spectacular character of the observations, and also because a physiological rationale can be speculated upon, we feel entitled to carefully submit that desogestrel could restore chemosensitivity in CCHS.

4.1. Physiological speculations

The pathophysiology of CCHS has recently gained new insights from studies conducted in knock-in mice carrying a 7 alanine expansion of the Phox2B gene. Histological analyses have shown that the medullar neurons of the parafacial respiratory group and/or the retro-trapezoid nucleus, two structures essential for ventilatory rhythmogenesis and chemosensitivity, are missing in these animals (Dubreuil et al., 2008). Their absence is regarded as the explanation of the ventilatory phenotype.

With this in mind, three notions must be emphasized to speculate about the mechanism by which desogestrel could explain our observations.

Firstly, ventilation is profoundly depressed during sleep in patients with CCHS but is generally not completely abolished; some degree of residual ventilatory activity remains. It is thus not aberrant to imagine that ventilation can be stimulated, even during sleep. As a matter of fact, this has been demonstrated by Gozal and Simakajornboon (2000), who observed a rise in ventilation during passive motion of the extremities. This was interpreted as illustrating the activation of mechanoreceptor-afferent pathways.

Secondly, several CO_2-responsive structures, like the locus ceruleus and the nucleus of the solitary tract, persist in Phox2B mutant mice (Dubreuil et al., 2008). The hypothalamus also contains CO_2-sensitive neurons (Williams et al., 2007) and its presence is a necessary condition of the progesterone-induced ventilatory rise (Bayliss and Millhorn, 1992). It does not seem to be affected by PHOX2B mutations, according to functional magnetic resonance imaging studies of the brain response to CO_2 in patients with CCHS (Harper et al., 2005).

Thirdly, progestins may also modulate ventilation through the peripheral chemoreceptors and the nucleus of the solitary tract (Pena and Garcia, 2006), that are unaltered in Phox2b mutant mice (Dubreuil et al., 2008).

Taken together, these elements make it not implausible that progestins could induce respiratory neuroplasticity and stimulate or activate "alternative" chemosensitive neural circuits. Under this hypothesis, the lack of pregnancy-related ventilatory improvement in patients with CCHS (Sritippayawan et al., 2002) would mean that natural progesterone is not potent enough to trigger these circuits. In contrast, our observations suggest that desogestrel could achieve this result, possibly because of its potency. Its binding affinity for the progesterone receptor is indeed approximately three times that of the natural hormone (Wiegratz and Kuhl, 2004).

4.2. Implications and perspective

The ventilatory response to CO_2 was obvious and reproducible in our two patients, but they were studied only when awake. We therefore do not know whether or not this response persisted during sleep, and if so we do not know if its magnitude would have been sufficient to allow the patients to sleep without their mechanical ventilator. The clinical relevance of our findings therefore remain to be determined, even if our observations are corroborated. Of note, a recovery of chemosensitivity that would be insufficient for ventilator weaning but sufficient to restore respiratory-related interoceptive alarms in the event of deep hypoventilation would still be of enormous clinical value. It would indeed confer protection against hypoventilation-induced tissue hypoxia.

We are aware that definitive conclusions cannot stem from the study of only two cases, but they seem to be the first documented instances of chemosensitivity recovery in CCHS. They therefore have strong proof of concept value, in the perspective of a simple pharmacological treatment of CCHS. A clinical trial is warranted, both for corroboration and to determine the extent of putative clinical benefits derived from reinstating ventilatory chemosensitivity in this disease.

Conflicts of interest

None declared.

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