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Congenital central hypoventilation syndrome (Ondine's curse syndrome) in two siblings: delayed diagnosis and successful noninvasive treatment

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Abstract Congenital central hypoventilation syndrome (CCHS, Ondine's curse syndrome) is a rare respiratory disorder; less than 100 cases have been reported. Familiality of the disease has been discussed, but only few familial cases have been reported so far. In this report we describe the occurrence of CCHS in two male siblings. Diagnosis was established only at the age of 4 years in the first case, although the patient had disease related symptoms since early infancy. The second patient was one of dizygotic twins, he was diagnosed with CCHS at the age of 8 months. Up to that age only moderate desaturations had been observed. The other twin was unaffected by the disease. Both patients were successfully treated by nocturnal positive-pressure ventilation via a specially adapted face mask. They show satisfactory physical and neurologic development.

Conclusion Our cases support the assumption of familiality in CCHS although the mode of inheritance remains to be clarified. Polygraphic recordings including capnography should be performed in siblings of CCHS patients early in life in order to avoid secondary complications. Noninvasive treatment by ventilation via special face masks is feasible.

Key words Congenital central hypoventilation syndrome (Ondine's curse syndrome) · Siblings · Polygraphic recordings

Abbreviations *CCHS* congenital central hypoventilation syndrome · $ETCO_2$ end-tidal carbon dioxide · *REM* rapid eye movement · *HD* Hirschsprung disease

Introduction

Congenital central hypoventilation syndrome (CCHS, Ondine's curse syndrome) is a respiratory disorder characterised by the absence of sufficient chemoreceptor control. The site of disturbance (peripheral chemoreceptors, central chemoreceptors, CNS integration) has not been entirely clarified [2–6, 10, 11, 13, 14, 16, 22]. Several degrees of severity have been reported ranging from moderate hypoventilation during sleep to the necessity of continuous ventilation [12, 15, 19, 25, 27]. Less than 100 CCHS cases have been reported so far [1–13, 15–22, 24–27], and the incidence of Ondine's curse syndrome is estimated to be around 1/100,000 [26]. Most of the patients are able to breathe sufficiently during waking, but require ventilation support during sleep (positive-pressure ventilation, negative-pressure ventilation or diaphragm pacer [12]).

Only few familial cases have been published [6, 7, 9, 13]. In this report we describe the occurrence of CCHS in two siblings and a method of noninvasive treatment. Possible consequences for further CCHS cases are discussed.

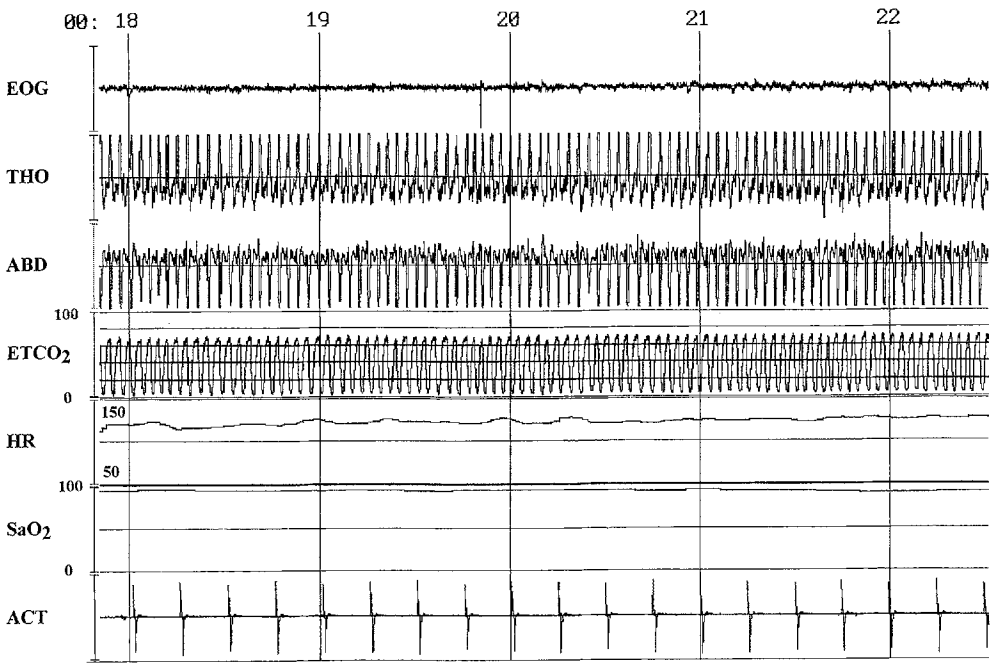

Fig. 1 Period of hypoventilation during non REM sleep. Oxygen saturation is in the normal range, but $ETCO_2$ is elevated (around 68 mm Hg). *EOG* electrooculogram, *THO* thoracic respiration activity, *ABD* abdominal respiration activity, *HR* heart rate (beats per minute), $ETCO_2$ capnography (mm Hg), SaO_2 oxygen saturation (%), *ACT* activity (body movements; the periodical spikes are calibration spikes)

Case reports

Case 1

The patient was born in Afghanistan. Since birth repeated cyanosis was observed by parents, the first severe cyanotic attack occurred at the age of 4 months and led to clinical investigation at an outside hospital. Repeated mechanical ventilation for several weeks was necessary. Polygraphic recordings after weaning from the respirator showed the absence of prolonged apnoeas, but several blood gas analyses revealed elevated PCO_2 values during sleep. However, end-tidal carbon dioxide ($ETCO_2$) monitoring was not performed and lung volumes were not assessed during sleep. Repeated bronchoscopies showed normal airways and echocardiography showed signs of pulmonary hypertension. Therapeutic trials with nifedipine, digoxin and aminophylline led to no clinical improvement. In the 3rd year of life repeated seizures associated with severe hypoxaemia (up to ten attacks per day) occurred and severe psychomental retardation was observed. At the age of 4 years the patient was referred to the Children's Hospital Klagenfurt. A thorough investigation showed pronounced hypoventilation during sleep associated with hypercapnia and repeated hypoxaemia. The diagnosis "Ondine's curse syndrome" was established. As the parents refused tracheostomy in their child, a face mask was adapted for mechanical ventilation during sleep. Since then a marked improvement of the clinical and neurological status was observed, seizures disappeared. Parents were trained to fix the mask and to operate the respirator, and the patient was discharged from hospital after several months. Since then mechanical ventilation during sleep has been performed at home without major problems. The 8-year-old patient is able to attend a special education class at a regular school.

Case 2

The brother of case 1 was delivered without problems as one of two dizygotic twins. Both twins were repeatedly (but not continuously) monitored by pulse oximetry during sleep, and repeated moderate desaturations were observed in this sibling. No polygraphic recordings were performed at that time. At the age of 7 months neurological development was worse when compared to his twin brother. At the age of 8 months repeated seizures associated with cyanosis occurred, and the infant was referred to the Children's Hospital Graz after a severe cyanotic attack. Polygraphic recordings during sleep showed varying hypercapnia ($ETCO_2$ between 52 and 113 mm Hg, Fig. 1) and hypoxaemic phases (SaO_2 minimum 38%).

Lung function testing during waking and bronchoscopy revealed no abnormalities explaining the clinical symptoms, echocardiography showed moderate signs of pulmonary hypertension. Registration of spontaneous breathing during sleep revealed varying degrees of hypoventilation. Hypoventilation was due to reduced tidal volume (1.8–7.4 ml/kg) whereas respiration frequency was in the normal range (20–33/min). Hypoventilation was varying in a wide range on different days and during different sleep cycles; in general hypoventilation was more pronounced during non rapid eye movement (non REM) sleep than during REM sleep.

Hypercapnic (up to 87 mm Hg tc-PCO_2) and hypoxaemic (down to 69% SaO_2) challenge tests showed following results: acute hypercapnia and acute hypoxaemia led to respiratory and arousal responses thus confirming the presence of chemoreceptor control mechanisms. However, these responses were not in the normal range (change in minute ventilation < 9 ml/kg/min/mm CO_2, unchanged tidal volumes during hypoxaemia associated with increased respiration frequency, pathological arousal threshold [22, 23]). Gradual hypercapnia and hypoxemia induced by rebreathing techniques did not lead to adequate respiratory and arousal responses (Fig. 2). These findings are in accordance with earlier investigations in CCHS patients [2–5, 11, 16, 17, 22, 25].

The patient was treated with positive-pressure ventilation via a special face mask during sleep (Fig. 3). Despite the patient's young age the face mask was quite well tolerated. At an age of 14 months neurological development of the patient had normalised and is now (at an age of 20 months) comparable in the patient and his unaffected twin brother.

Evaluation of family history

The family tree drawn by parents showed 44 first and second degree relatives. One uncle (on the mother's side) of our patients suf-

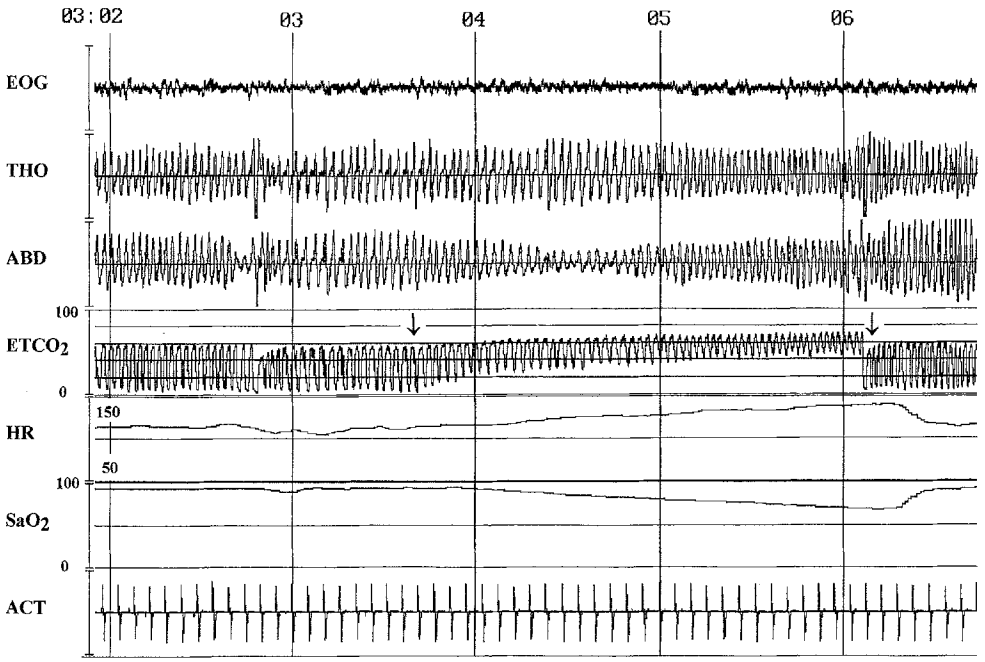

Fig. 2 Simultaneous hypercapnic and hypoxic challenge test by rebreathing technique during non REM sleep. *Arrows* indicate onset and end of rebreathing. The challenge test leads to an increase of $ETCO_2$ from 58 to 71 mm Hg and a decrease of SaO_2 from 92% to 68%. Accelerated respiration frequency (typical response pattern in CCHS patients [3, 17]) and increasing heart rate are observed. However, tidal volumes (simultaneously recorded by pneumotachography not shown in this figure) remain almost unchanged. No adequate arousal response is observed

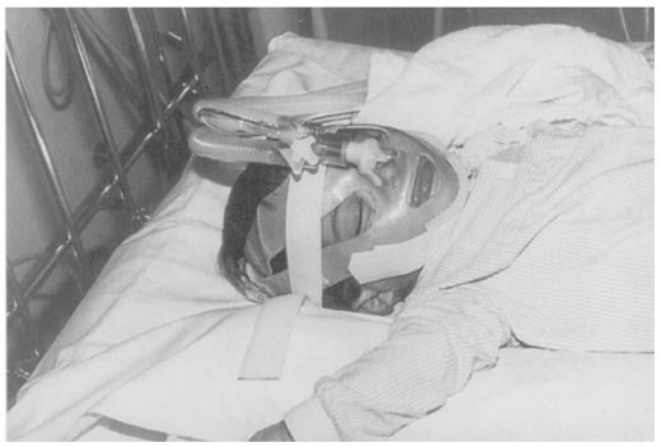

Fig. 3 Case 2 at the age of 12 months. The patient is ventilated during sleep by positive-pressure ventilation via a specially adapted face mask

fered from an „unknown disease" since early infancy and was severely compromised by neurodevelopmental retardation. He died suddenly at the age of 20 years. No other cases of possibly CCHS related disorders or deaths were reported in the family tree. Polygraphic investigations of the twin brother of patient 2 showed no abnormalities.

Discussion

Hypoventilation in CCHS is a consequence of low tidal volumes in most cases [4, 25] and is most pronounced during non REM sleep [2, 5, 21]. Disturbed central and peripheral chemoreceptor function has been described in CCHS patients [2, 4, 10, 11, 25], but recently an inadequate central integration of chemoreceptor signals has become most likely to be responsible for the disease [16]. An association with other autonomic disorders, especially Hirschsprung disease (HD), has frequently been observed and has led to the assumption of a common cause (neurocristopathy) of these disorders [6, 7, 18, 24, 26].

The outcome of CCHS patients is strongly dependent on the time of diagnosis. Whereas patients with delayed diagnosis frequently show neurodevelopmental disorders and other secondary complications (pulmonary hypertension, cor pulmonale, seizures etc. [1, 12, 25]), an early diagnosis can markedly improve the situation [12, 15] and is mandatory for a good long-term medical and psychosocial outcome.

It has been repeatedly discussed whether CCHS is an inherited disorder [6, 9, 18, 24, 26, 27]. Whereas some earlier reports describe disturbed chemosensitivity in relatives of CCHS patients and assume a possible subclinical manifestation of the disorder in relatives [2, 14], other reports describe normal chemoreceptor function in relatives of CCHS patients and reject any kind of inheritance [13]. Recent calculations make familiality of CCHS most likely, especially when combined with HD [26]. Five pairs of affected siblings have been reported so far [6, 9, 7, 13, 25]. In three of them, the affected sibs also had Hirschsprung disease [6, 7, 25].

Our two cases represent the sixth reported pair of affected siblings and the second without evidence of HD. These additional cases make familiality of CCHS (also without HD) more likely although the mode of inheritance remains to be clarified.

Recently, in CCHS families an intriguing high incidence of SID has been reported [26]; one may speculate that some cases of sudden (infant) deaths could in fact be undiagnosed CCHS victims.

To summarize parents of CCHS patients should be informed that the recurrence risk is higher than the „random risk". Empirically, a recurrence risk < 5% can be cited in family counselling [26]. Furthermore, the occurrence of CCHS in a family should lead to early polygraphic investigations in subsequent siblings. Investigations should include long-term CO_2 measurements in order not to miss hypoventilation during phases of normal SaO_2 levels. In case of hypoventilation early treatment should be established in order to avoid secondary complications like neurological compromise and pulmonary hypertension. Positive-pressure ventilation via a special nasal [8] or face mask provides a noninvasive alternative to tracheostomy or diaphragm pacer.

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