Respiratory Medicine (1996) **90**, 571–574

Temporary obstructive apnoea syndrome attributed to cryptococcus (meningo) encephalitis

B. BUYSE*‡, C. GYSBRECHTS†, E. MICHIELS*, G. VERHOEF† AND M. DEMEDTS*

*Departments of *Pneumology and †Haematology, University Hospital Gasthuisberg, Catholic University, Leuven, Belgium*

Introduction

The present case report describes a patient treated for leukaemia in whom the tentative diagnosis of a cryptococcal (meningo) encephalitis was made. The principal manifestation of this (meningo) encephalitis was a temporary obstructive sleep apnoea syndrome (diagnosed by a polysomnographic study).

Case Report

In this 45-year-old man, a diagnosis of a non-Hodgkin lymphoma (Stadium 2B) had been made 2 yr previously, and he was cured after treatment with cytostatic drugs and radiotherapy on the mediastinum. Five months ago, he developed a secondary acute myeloid leukemia (Type M2). According to FAB criteria, remission–induction therapy consisted of idarubicine, ara-C, VP-16 and novantrone, and his complete remission was consolidated with an autologous bone marrow transplantation. The conditionary regime consisted of cyclophosphamide and busulphan and he received his bone marrow infusion on 21 November 1994. Subsequently, he developed several septicemias (*Escherichia coli* and coagulase negative staphylococci), liver dysfunction probably due to veno-occlusive disease and a painful haematuria due to traumatic bladder canulation and thrombopenia. At the end of December 1994, the patient manifested symptoms compatible with encephalopathy (loss of decorum, perplexity).

In the night of 7 January 1995, snoring and obstructive breathing during sleep was first noted. Thirty-six hours later, the patient demonstrated a variable level of consciousness. When awake, he answered questions adequately and did not demonstrate any neurological abnormality, nor abnormalities in his breathing pattern. When not stimulated, he fell asleep immediately, then presenting an obstructive breathing pattern with heavy snoring and apnoeas. The patient underwent a detailed clinical neurological investigation. No signs demonstrating lateralizations nor cranial palsies were found; only a nystagmus was present. On rhinolaryngological investigation, no abnormalities in pharynx or larynx were visualized. At that time, his treatment consisted of teicoplanine, ofloxacine, ceftazidime, mesna and piritramide for painful haematuria (piritramide was started 14 days previously, mean dose 40 mg day^{-1}, dose not raised during the last days), and diuretics for the veno-occlusive disease with ascites. The X-ray of the chest was normal with a normal cardiac configuration and without signs of cardiac decompensation. Blood pH value was normal (7·4), as were $PaCO_2$ (42·6 mmHg), HCO_3 (26·5 meq l^{-1}), sodium (137 meq l^{-1}), potassium (3·5 meq l^{-1}) and phosphorus (3·6 mg dl^{-1}). There was pancytopenia (with a haemoglobin of 6·9 g dl^{-1}, a leukopenia of 2300 mm^{-3} and thrombopenia of $54 \cdot 10^9\ l^{-1}$), a normal renal function and slightly elevated liver enzymes; total bilirubin 4·9 mg dl^{-1} (normal values 0 2–1), alkaline phosphates 348 U l^{-1} (normal values 90–260), glutamyl transferases 66 U l^{-1} (normal values 11–50) and ammonia 57 μmol l^{-1} (normal values 12–55). A polysomnographic study (Fig. 1) was performed between 1 pm and 3.30 pm, which revealed 97 obstructive apnoeas, six central apnoeas, 13 mixed apnoeas and 20 hypopnoeas. Each respiratory event was followed by marked desaturation. Oxygen desaturation (<90%) was present in 47% of the time, with a minimum saturation of 74·5%. Analysis of the EEG, EOG and EMG patterns showed that the consciousness of the patient changed continuously between being awake and light sleep. A computed tomographic (CT) scan of the brain demonstrated a widened ventricle system, clearly wider

Received 22 May 1995 and accepted in revised form 22 March 1996.

‡Author to whom correspondence should be addressed at: Department of Pneumology, University Hospital Gasthuisberg, Herestraat, 49, B-3000 Leuven, Belgium.

0954-6111/96/090571+04 $12.00/0

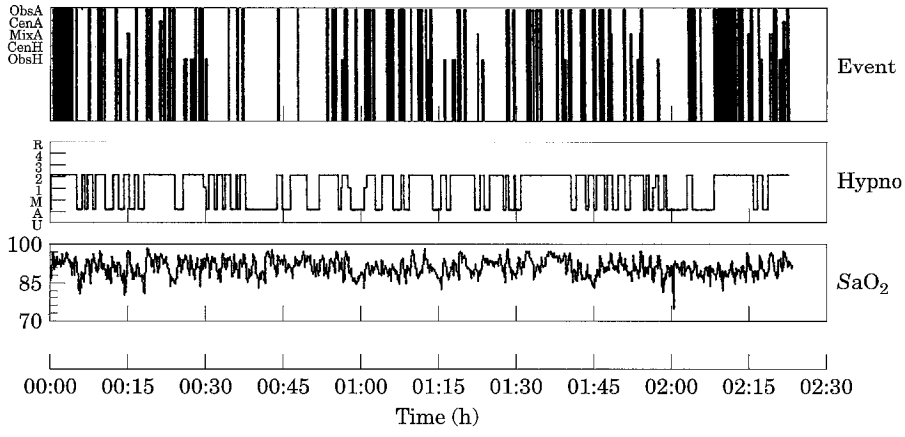

Fig. 1 Results of the first polysomnography (registered on 'Sleepwalker — Medatec'). Event, apnoea (cessation of air flow for at least 10 s) or hypopnoea [reduction of air flow (at least 50%) for at least 10 s with desaturation (at least 4%)]; Obs A, obstructive apnoea; Cen A, central apnoea; Mix A, mixed apnoea; Cen H, central hypopnoea; Obs H, obstructive hypopnoea; Hypno, hypnogram; R, REM sleep; 1,2,3,4, non-REM sleep, Stadiums 1,2,3,4; A, awake; U, unknown; SaO_2, transcutaneous saturation (%).

than the CT scan performed 2 months earlier. The nuclear magnetic resonance scan only showed totally aspecific lesions in the semi-oval centre. A lumbal puncture demonstrated an elevated intracerebral pressure (500 mmH_20), the liquid was clear with a normal protein and glucose concentration. The cytosis was 0·8 mm^{-3}. Gram- and Ziehl-Nielsen-stainings were normal; cultures of lumbal liquid showed no growth of micro-organisms, the serology for herpes and toxoplasma gondii was also normal. Cytomegalovirus isolates on buffy coat, lumbal liquid, urine and throat swabbing were also negative. The cryptococcal antigen detection test (Latex, Crypto Antigen System Kit-Immy) performed on lumbal liquid demonstrated a titre of 1/1. Treatment with amfotericine B (60 mg day^{-1}) and fluconazol (parenteral administration of 400 mg day^{-1}) was started. Piritramide was stopped. Three days later, although the patient was still sleepy, no obstructive breathing was noted anymore. The intracerebral pressure was lowered to 250 mmH_20 and the cryptococcal antigen titre was 1/2. The haemoglobin level was 7·7 g dl^{-1} at that time. A control polysomnographic study was performed (Fig. 2) on 23 January 1995. At that time, the haemoglobin level was 9 g dl^{-1}. Only one hypopnoea was noted and no desaturation (saturation below 90%) was seen. A cryptococcal antigen detection test on lumbal liquid was also performed 3 weeks after the first analysis, and demonstrated a titre of zero, and the intracerebral pressure was lowered to 190 mmH_20 (normal value).

Discussion

The present case report describes a patient demonstrating an obvious obstructive sleep apnoea syndrome, which was attributed to a cryptococcal (meningo) encephalitis. After treatment with amfotericine B and fluconazolum, the apnoea problem disappeared, and a control polysomnographic study performed 14 days after the onset of the apnoea syndrome showed that no apnoeas were present. The authors are aware that the cryptococcal antigen titre is rather low (1/2) to ascertain the diagnosis of cryptococcal (meningo) encephalitis. Also, a normal cerebrospinal fluid (CSF) (with normal glucose and protein concentrations and leucocyte counts) might be surprising, although the absence of abnormalities of CSF are seen frequently in AIDS patients with cryptococcal infections, and occasionally in other patients (2). The present patient had immunosuppressive medications which probably contributed to the absence of proteins and pleocytosis. Nevertheless, the authors think that this diagnosis is very probable because (1) there was a typical compatible constellation of symptoms and signs (encephalopathy, a widened ventricle system and a markedly elevated intracerebral pressure), (2) no other germs were detected, and (3) there was a clearly favourable effect of amfotericine B and fluconazolum; clear clinical response, an objective lowering of the intracerebral pressure after treatment for 3 days (from 500 to 250 mmH_20), with normalization (190 mmH_20) after treatment for 3 weeks and a normalization of the

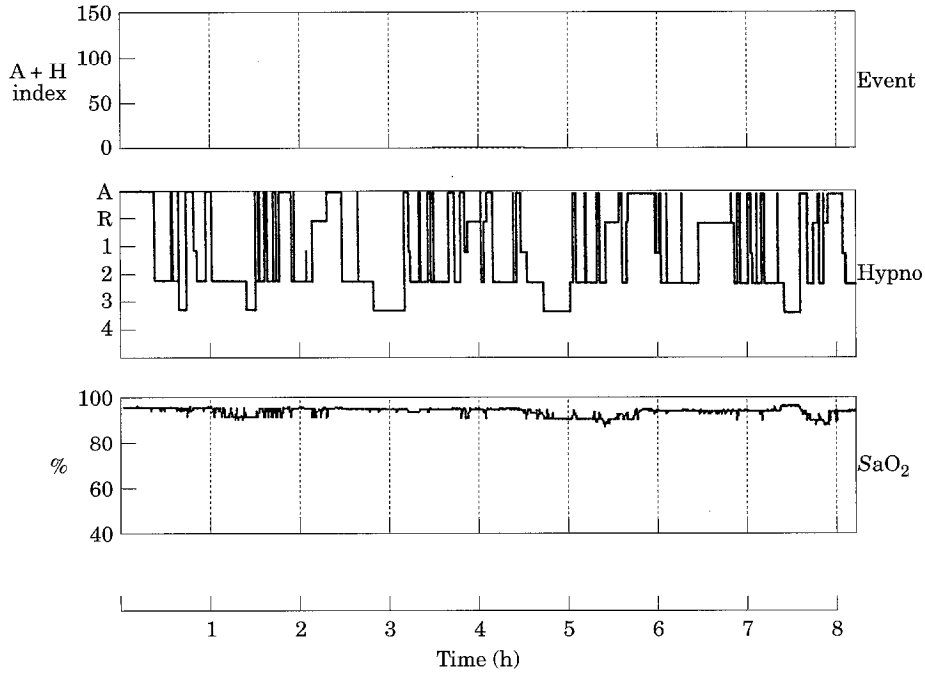

Fig. 2 Results of the control polysomnography (registered on 'Somnostar 4100 — Sensormedics'). Event, apnoea (cessation of airflow for at least 10 s) or hypopnoea [reduction of airflow (at least 50%) for at least 10 s with desaturation (at least 4%)]; A+H index, number of apnoeas and hypopnoeas h^{-1}; Hypno, hypnogram; R, REM sleep; 1,2,3,4, non-REM sleep, Stadiums 1,2,3,4; A, awake; SaO_2, transcutaneous saturation (%).

cryptococcal antigen titre 3 weeks after treatment commenced (cryptococcal antigen titre=0). The authors are not aware of other published cases of apnoea caused by cryptococcus neoformans, nor of apnoea caused of infections in adults, while in young children, apnoea is a well-known manifestation of infections especially by respiratory syncytial virus (RSV). Church *et al.* (3) mentioned that 18% of all infants admitted with RSV developed apnoea. Other casuistic observations suggest that infections other than RSV may affect vital centres and cause apnoeas in babies; listeria monocytogenes (4), echovirus type 2 (4) and enterococcal infection (5).

Theoretically, the abnormal breathing could be the resultant of muscle weakness, although no major metabolic derangements (almost normal hepatic enzymes, normal electrolytes, no disturbance in acid-base status), except the presence of anaemia, were found in the present patient (haemoglobin level of 6·9 g dl^{-1}). Theoretically, this anaemia may also have played a role in the apnoea syndrome. On one hand, anaemia may have reduced respiratory muscle force, but on the other hand could also have influenced the respiratory control system. Anaemia has been shown to increase the duration of apnoeic pauses elicited by laryngeal stimulation in piglets (6), to enhance the peripheral chemoreceptor-mediated response to hypoxia in goats (7), and to blunt the chemoreceptor response to carbon dioxide in adults (8). In a retrospective study published by Poets *et al.* (9), the relationship between anaemia and apnoea was investigated in 72 infants referred for assessment and home monitoring following an apparently life-threatening apnoea event. Significantly more infants than expected had haemoglobin levels below the mean. In the present case, haemoglobin levels also tended to be higher when apnoeas disappeared (Hb 6·9 g dl^{-1} when symptomatic; Hb 7·7 g dl^{-1} 3 days later when the patient was sleepy, but no longer demonstrated apnoeas; Hb 9 g dl^{-1} when the polysomnographic re-evaluation was performed and demonstrated normalization).

The role of piritramide must also be discussed in the aetiology of this apnoea problem. Piritramide is known to enhance the severity of obstructive sleep apnoea, by promoting upper airway instability by selectively reducing the innervation to the upper airway dilatator muscles (10). Although piritramide may have played an additional role in this case, the authors argue that it is not the principal cause.

Firstly, the patient used piritramide (even in higher dose) for several weeks without any problem, and secondly, the control polysomnographic study showed no evidence of an (even silent) obstructive sleep apnoea problem, despite the fact that piritramide was restarted.

Conclusion

This case report describes a temporary obstructive sleep apnoea syndrome in relationship with a cryptococcal infection. Although infections (especially RSV infections) may cause apnoea in children under 1 year of age, the authors are unaware of such a problem in adults. In particular, no case of apnoea in relation to cryptococcus neoformans infection was found by the authors. It is also of interest to emphasize the possible role of anaemia in this apnoea problem, although such a relationship has only been described in infants.

References

1. Rechtschaffen A, Kales A (eds). *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep States of Human Subjects.* DHEW NIH Publication 204. Washington DC: US Government Printing Office, 1968.
2. Mandell, Douglas, Benett. *Principles and Practice of Infectious Diseases.* Churchill Livingstone, 4th Edition, 1995, pp. 2331–2340.
3. Church N, Anas N, Hall C, Brooks J. Respiratory syncytial virus-related apnea in infants. *Am J Dis Child* 1984; **138:** 247–250.
4. Johnston D, Kuzemko J. Virus-induced apnoea and theophylline. *Lancet* 1992; **340:** 1352.
5. Dobson S, Baker C. Enterococcal sepsis in neonates: features by age at onset and occurence of focal infection. *Pediatrics* 1990; **85:** 165–171.
6. Lee J, Downing S. Laryngeal reflex inhibition of breathing in piglets: influences of anemia and catecholamine depletion. *J Appl Physiol* 1980; **239:** 25–30.
7. Santiago T, Edelman N, Fishman A. The effect of anemia on the ventilatory response to transient and steady-state hypoxia. *J Clin Invest* 1975; **55:** 410–418.
8. Vijayaxmi N, Ponde J, Gupta S, Guleria J. Peripheral chemoreceptor insensitivity in chronic severe anaemia. *Respiration* 1978; **35:** 37–39.
9. Poets C, Samuels M, Wardrop C, Picton-Jones E, Southall D. Reduced haemoglobin levels in infants presenting with apparent life-threatening events — a retrospective investigation. *Acta Paediatr* 1992; **81:** 319–321.
10. Rafferty T, Ruskis A, Sasaki C, Gee J. Perioperative considerations in the management of tracheostomy for the obstructive sleep apnea patient. *Br J Anaest* 1980; **52:** 619–621.