Delayed Respiratory Failure During the Treatment of Myxedema Coma

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Abstract

Three male patients (aged 41, 71 and 65 years) with untreated severe hypothyroidism of long duration were in a state of coma. This had been preceded by respiratory symptoms accompanied by hypoxemia and hypercapnea. There were also various chest radiographic findings. All the patients were treated with mechanical ventilatory assistance, circulatory support and i.v. administration of high doses of l-triiodo-thyronine (T₃) during the early period of treatment. None of the patients showed any serious cardiac ill-effects immediately or a few days following the intravenous administration of T₃. In spite of the stabilisation of vital signs and improvement in arterial oxygenation, the patients remained in a comatous or semicomatous state for the first few days. During the second week, the condition of their lungs deteriorated and prolonged respiratory failure ensued with fever, rales, excessive bronchial secretion, homogenous densities in the chest radiograms and persistent hypoxemia even though mechanical ventilatory treatment was continued. The implications of this delayed respiratory failure during the treatment of myxedema coma are discussed.

Myxedema coma is a rare and life-threatening complication of long-standing, severe hypothyroidism. Its occurrence at present is very infrequent probably because of early detection of clinical and subclinical hypothyroidism by wide application of measurement of serum thyroid and thyrotropic hormones by radioimmunoassays (RIA). Rapid thyroid hormone replacement, such as either l-thyroxine (T₄) or l-3, 3', 5-tri-iodo-thyronine (T₃), is recommended since the depleted extra-thyroidal pool of thyroid hormone must be refilled promptly to save the life of victims (Cats and Russel, 1961; Holvey et al., 1964). In addition, circulatory support, adrenocorticosteroids, mechanical ventilatory assistance and careful monitoring of cardio-pulmonary function presumably improve the prognosis of this complication.

In the present report, the clinical course of each of three patients with myxedema coma is described. At the time of their admission to hospital, they were in a state of coma, accompanied by acute respiratory failure and various radiologically detected chest abnormalities. All the patients were given mechanical ventilatory assistance, careful monitoring and management of circulation, and high doses of parenteral thyroid hormone replacement. In spite of stabilisa-
tion of vital signs and transient improvement in arterial oxygenation within a few days of therapy, they remained in a state of coma or semicoma followed by prolonged respiratory failure even after the end of the first week. Two of them succumbed to it and one necessitated mechanical ventilatory assistance for 4 months.

Case Summaries

Case 1.

41-year-old man, a recluse since his late teens, was brought to the hospital by his family after he lost consciousness. Following development of upper respiratory illness one week prior to admission, his mentation became progressively obtunded into deep coma. The man was of short stature and had disproportionately short extremities. His respiration was shallow and infrequent and the blood pressure 78 mmHg by palpation. Dry, scaly skin, puffy face, distant heart sound, and distended abdomen were noticed. The peripheral blood showed mild normocytic anemia. The BUN was 17.6 mg/dl, creatinine, 2.0 mg/dl, and sodium, 139 mEq/L. The partial pressures of the arterial oxygen and carbon dioxide (PaO₂, PaCO₂) were 39.9, 46.2 mmHg, respectively. The chest roentgenogram showed an overt cardiomegaly, atelectasis of the left lung and pleural effusion on the same side. The patient was initially given mechanical ventilatory treatment, intravenous infusion of vasopressor, and hormonal replacement with desiccated thyroid, 20 mg per day using a nasogastric tube, along with hydrocortisone, for a presumptive diagnosis of myxedema coma. He remained semicatomatic for the first 3 days, with his blood pressure kept at a systolic level of 100 to 120 mmHg by means of a vasopressor. The daily urine output exceeded 1,500 ml/day and was above the total intake. The central venous pressure was less than 10 cm H₂O. PaO₂ increased gradually to 79 mmHg by maintaining a higher fraction of inspired oxygen (FiO₂). The initial serum thyrotropin (TSH) was 227 µU/ml, while T₄ and T₃ of the same serum were below the sensitivity level of the respective RIA (Serum thyroid and thyrotropic hormones were measured with RIA kits. The normal ranges for T₄, T₃ and TSH were 8.2–14.5 µg/dl, 0.96–1.92 ng/ml and less than 8 µU/ml, respectively). The serum thyroid and thyrotropic hormone values in the early period of treatment of this patient and 2 others are shown in figure 1. It was decided that he should be given T₃ intravenously, prepared by the method of Nickerson et al. (1960), in the amount of 150 µg on the third day and two doses of 75 µg each on the 4th day, followed by the administration of slowly increasing doses of desiccated thyroid via a nasogastric tube. There appeared to be no serious cardiac abnormalities immediately or for the first few days following the i.v. doses of T₃. By the latter part of the first week, he became responsive to simple oral commands, the blood pressure so stabilised that a vasopressor was no longer needed and the PaO₂ remained above 60 mmHg with FiO₂ 70%. During the second week, his temperature stayed above 38°C, respiration became laborious with increased rales and excessive tracheobronchial secretion. The PaO₂ deteriorated and leucocytosis over 10,000/mm³ persisted. The chest radiograms showed a gradual reduction in cardiac size and left pleural effusion but, at the same time, there was a gradual development of bronchopneumonia in the right lung. Escherichia coli along with other gram-negative bacilli were cultured from the sputum. His pulmonary condition which had temporarily improved during the third week, started a course of progressive deterioration. He died from sudden cardiac arrest on the 26th day. Autopsy was not allowed.
Case 2.

A 71-year-old man who had suffered from primary hypothyroidism diagnosed 2 years previously, was placed on thyroid replacement for a short period. He had a chronic productive cough in recent years. For 2 weeks prior to admission, he became slowly obtunded, followed by progressive reduction in oral intake. He was admitted to hospital because of difficulty in discharging thick sputa almost to the point of choking. He was a man of normal development of pale complexion and in semi-comatous state. Only a weak pulse was palpable and the axillary temperature was below 35°C. He had typical stigmata of long-standing hypothyroidism. The blood count showed mild anemia of macrocytic indices and normal white cell count. The total serum protein was 7.3 g/dl with an A/G ratio of 0.9, cholesterol, 150 mg/dl, glucose, 65 mg/dl.
PaO$_2$, 56.7 mmHg, and PaCO$_2$, 51.7 mmHg. The initial chest radiogram showed moderate cardiac enlargement and emphysematous lungs. The EKG showed low-voltage QRS complexes at a regular rate of 48/min. He was placed on mechanical ventilatory treatment, kept under a thermoblancket, and given vasopressor intravenously. His vital signs stabilised slowly during the following 20 hours. On the second day, he was still in a semi-comatous state. The PaO$_2$ remained around 90 mmHg with FIO$_2$ 40%. He was given 50 µg of T$_3$ intravenously, then 25 µg every 8 hours 3 times on the second and third days and then maintained on 150 µg of T$_4$ once daily via a nasogastric tube because of initial serum T$_4$ was less than 0.5 µg/dl. No immediate serious cardiac effects were observed after the rapid T$_3$ administration. The urine output for the first 2 days was about 1,200 ml/day. After pericardiocentesis on the third day, the urine output gradually increased but remained insufficient to maintain a negative water balance. In the latter half of the first week, he became somewhat conscious and was able to respond to simple questions. In the second week, his respiration became labored with increased rales and excessive purulent tracheobronchial secretion. Mixed gram-negative organisms grew out of a sputum culture. The chest radiograms showed homogeneous densities with alveolograms in the right middle and lower lungs, effusion in the interlobar fissure and multiple Kerley B lines. The PaO$_2$ dropped to 68 mmHg despite the FIO$_2$ 100%. During the latter half of the second week, his temperature remained above 38°C and leucocyte count above 10,000/mm$^3$. The urine output decreased, subcutaneous edema gradually increased and homogenous densities appeared in the upper part of both lungs. The patient’s blood pressure grandually decreased and he died on the 12th day. Autopsy was not permitted.

**Case 3.**

A 65-year-old man was admitted to the hospital for unresponsiveness. He had been unemployed since about the age of 40, owing to quick fatiguing. About one week before admission, he had developed hoarseness, facial edema and reduced urine output. Then, he became dyspnecic and obtunded progressively. An examination showed the man to be well-developed, markedly edematous and in a semi-coma with a blood pressure of 104 mmHg systolic, and 72 mmHg diastolic, pulse 102/min and axillary temperature 35.7°C. Other physical findings were consistent with long-standing myxedema. The hemoglobin was 17.4 g/dl, hematocrit 50% and the white cell count, 13,000/mm$^3$. The blood chemistry was unremarkable. The PaO$_2$ was 38.1 mmHg and PaCO$_2$, 60 mmHg. The chest radiogram revealed cardiomegaly, emphysematous lungs, atelectasis of the right middle lobe and scattered micronodular densities in both lower lungs. EKG showed low-voltage complexes at a rate of 80/min. Serum T$_4$, T$_3$ and TSH were 0.4 ng/dl, 0.4 ng/ml and 52 µU/ml, respectively, He was placed on mechanical ventilatory assistance with which PaO$_2$ was kept above 100 mmHg with FIO$_2$ 40%. The blood pressure could be maintained without a vasopressor. The urine output was 2,480 ml during the first 6 hours and subsequent urine output was adequate to maintain a negative water balance for the first week. Following a reduction in serum T$_4$ and T$_3$, he was administered high doses of intravenous T$_3$, totalling 125 µg over a period of 2 days, along with hydrocortisone. He was then given 150 µg of T$_4$ through a nasogastric tube. No significant cardiac abnormalities were observed following i. v. doses of T$_3$, immediately after or in the following several days. He became responsive to oral questioning although his attention span remained limited in the latter half of the first week. Low grade fever persisted and rales
were numerous. Tracheobronchial secretion remained excessive and became bloody around the 10th day. Proteus grew repeatedly from the sputum culture. He was treated with ampicillin, carbenicillin and amikacin. The atelectasis of the right middle lobe gradually cleared but micronodular densities increased in the right upper and bilateral lower lung fields and made these areas homogenously cloudy with multiple alveolograms at the time his condition was most serious. Weaning from the respirator was attempted on the 5th day without immediate ill-effects but on the 7th day, he went into apnea suddenly. Following this episode, the PaO₂ was barely maintained at around 60 mmHg with FIO₂ 100%. Because of a further reduction in PaO₂, positive end-expiratory pressure (initially 3 mmHg and maximum 8 mmHg) was employed in the 3rd week. During the middle of that week, his consciousness began to improve though he was somnolent during the day. At about this time, the urine output increased, remaining as much as 3,000 ml/day throughout the 4th week, during which time his temperature stayed between 37 and 39°C, tracheobronchial secretion abated and assumed a mucoid character. The chest radiograms showed moderate reduction in the cardiac silhouette and gradual clearing of homogenous densities in the lower lung fields. During the second month, he was alert but quite lethargic. He lost a great amount of subcutaneous edema. The temperature remained normal. With initiation of physiotherapy of the extremities and of respiratory muscles, gradual weaning from the respirator was started slowly enough to avoid fatiguing and continued until the patient was no longer dependent on it during the 4th month.

Discussion

There is no apparent established definition of myxedema coma in the literature. The term has been used in reference to impaired consciousness observed at the late stage of long-standing, untreated hypothyroidism. Although the cause of coma has not been fully determined in the case of thyroid hormone deficiency per se, or thyroprival cerebral, cardiac and/or pulmonary dysfunction, it is quite distinct from the cause of coma in hypothyroid patients occurring apparently as a result of stroke, shock or metabolic derangement in otherwise stable, untreated hypothyroidism. This has been shown by the data obtained from the three patients described above. Coma and respiratory failure were common to all three patients. Respiratory failure with CO₂ narcosis is considered to be a cause of myxedema coma (Nordqvist et al., 1960) and several such cases have been reported (Massumi and Winnicker, 1964; Buchanan et al., 1967; Buckle and Garfield, 1969; Boyd et al., 1969; Domms and Vassalo, 1973; Nicholis and Hunt, 1976) but this does not seem related to our patients since the CO₂ retention before therapy was only modest. Hypoxemia per se does not seem to be the cause of coma, either, since consciousness disturbance persisted following normalization of PaO₂ by mechanical ventilatory treatment for a few days. Respiratory dysfunction is known to accompany myxedema as a result of the reduced sensitivity of the respiratory center to hypoxemia and hypercapnea (Massumi and Winnicker, 1964; Domms and Vassalo, 1973; Zwillich et al., 1975), impaired bellow function of the respiratory muscles (Wilson and Bedell, 1960), and the obstruction of the upper airway (Yamamoto et al., 1977; Orr et al., 1981). Most of these abnormalities can be eliminated through adequate ventilatory treatment unless complicated by intrinsic lung diseases.
In our patients, however, the problem of delayed respiratory failure was encountered following initial therapy. There have not been many reports of the occurrence of such a problem (Nicholis and Hunt, 1976; Senior et al., 1971) and its pathogenesis remains obscure. There appear to be various direct causes for the development and persistence of the delayed respiratory failure. In our patients, a loss of consciousness was preceded by acute (case 1) and chronic (cases 2, 3) respiratory symptoms. The initial chest radiograms revealed atelectasis and pleural effusion in case 1, emphysema in case 2, and atelectasis and emphysema in case 3. Acute and/or chronic lung disease was an obvious condition prior to therapy in these patients. Excessive tracheobronchial secretion, persistence of fever and leucocytosis, homogenous densities in the chest radiograms and positive sputum culture of gram-negative bacilli indicate pneumonia probably due to gram-negative bacilli. The presence of subcutaneous edema, cardiomegaly, insufficient diuresis and pleural effusion, particularly in cases 2 and 3, indicate systemic and pulmonary congestion before and after initial treatment. Mechanical ventilatory assistance using a high concentration of oxygen was also detrimental to the lungs.

Although the prompt administration of thyroid hormone is recommended for treatment of myxedema coma, the choice of thyroid hormones, routes, amounts and intervals of administration presumably vary according to the patients' condition. The initial administration of doses of 50 to 210 μg of T₃, followed by T₄ given orally is recommended by several authors (Newark et al., 1974; Green, 1974; Hackenberg and Reinbein, 1978). The risk of cardiovascular complications has been stressed in case of rapid thyroid hormone replacement. Indeed, incidence of cardiac death attributable to rapid thyroid hormone administration has been reported (Anderson and Hausman, 1956; Bacci et al., 1981).

The rapid supply of T₃ per se does not seem responsible for development of delayed respiratory failure in our patients, for their serum T₃ levels rose transiently to the upper normal range at best following the i. v. doses and returned soon to a subnormal level when delayed respiratory failure set in (figure 1). Ladenson and coworkers (1982) observed a gradual improvement in selected parameters of cardiac, pulmonary and renal functions in patients with hypothyroidism within 7 days following by daily administration of 100 μg of T₄ intravenously. Although no immediate ill-effects were observed after rapid T₃ replacement, this may possibly have indirectly contributed to the development of delayed respiratory failure, placing strains on cardio-pulmonary units as a result of the need for additional oxygen for peripheral tissues about one week after the administration of thyroid hormones. Smaller orally administered doses of T₃, say 5 to 20 μg/day, were reported to be effective in saving the life of patients with myxedema coma (Murase et al., 1973; Graham and Harding, 1977; Maegaard et al., 1980). I feel that patients with myxedema coma would be helped more by using lesser amounts of thyroid hormones in the early period of therapy until the functional and structural alterations in pulmonary parenchyma and pulmonary defense mechanism against infection in long-standing myxedema are better understood. Pulmonary conditions should be carefully evaluated prior to therapy of myxedema coma to insure a better therapeutic outcome.

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References


