Lesson of the Week

Hyperthyroidism and acute bronchial asthma

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Bronchial asthma may be very mild, difficult to diagnose, but potentially lethal. We describe a severe case associated with thyrotoxicosis and the use of beta blockers, which should serve as a reminder of the important precipitating factors in this condition. It also serves to recall the words: "Primum, non nocere" (Hippocrates, 460-355 BC), or "I do not want two diseases—one nature made, one doctor made" (Napoleon Bonaparte, 1820).

Asthma may be very mild, at times hard to diagnose; beta blockade should be used only with great caution. An asthmatic who becomes thyrotoxic should be closely monitored for deterioration of the asthma

Case report

A 41 year old woman was admitted to the Royal Free Hospital in coma. In the previous six weeks she had lost weight, felt sweaty, had a tremor, and felt a lump in her throat. Three weeks previously her doctor had prescribed aminophylline 225 mg four times daily for dyspnoea and suspected asthma; she had had eczema in childhood. She was referred to another hospital with thyrotoxicosis, confirmed with a serum thyroxine concentration of 294 nmol/l (22·8 μg/100 ml). Five days before admission to our hospital treatment was started with propranolol 40 mg and carbimazole 15 mg, both thrice daily; the aminophylline was discontinued.

On the day of admission she developed worsening shortness of breath but had been doing "more than usual"; that evening she suddenly became blue and stopped breathing. She was given mouth to mouth respiration by a friend for 20 minutes until the ambulance arrived but she remained cyanosed throughout this period. Within 35 minutes she had arrived in the accident and emergency department, having been intubated with difficulty in the ambulance. She was cyanosed, not breathing, and not responding to pain. Initially she had a pulse rate of 100 per minute and her blood pressure was 150/100 mm Hg. She had considerable airways resistance to assisted ventilation, with a "silent chest" but after aminophylline 250 mg intravenously widespread rhonchi were audible. Her pupils (3/5) did not react to light and plantar responses were absent. There was a diffuse goitre.

Her goitre did not occlude the airway and after reintubation she was ventilated and given aminophylline, hydrocortisone, and broad spectrum antibiotics. She was transferred to the intensive care unit and two hours later had a generalised fit with fixed dilated pupils; she was given intravenous diazepam. On the second day she had signs of anoxic brain damage, with athetoid movements and no spontaneous respiratory effort. Nevertheless, her pupils were reacting to light, she was responding to pain, and corneal and gag reflexes were present. She had generalised brisk reflexes with finger jerks, bilateral ankle clonus, and extensor plantar responses. Her asthma was well controlled. An initial electroencephalogram taken 36 hours after the arrest was suggestive of anoxic brain damage but on the next day showed some improvement. She remained a further 10 days in the intensive care unit and for most of this time showed some resolving weakness of the right side. After being weaned off the ventilator she responded to questions but had no speech. She was given sodium iodide intravenously for her thyrotoxicosis, her initial thyroxine value being 216 nmol/l (16·8 μg/100 ml), falling to 109 nmol/l (8·5 μg/100 ml) after four days' treatment. Treatment with propylthiouracil 100 mg thrice daily and oral medication for asthma was started as soon as absorption was occurring.

In the general ward her progress continued satisfactorily with the aid of physiotherapy and speech therapy. There was no neurological deficit apart from slow thought processes; her voice was weak at the time of discharge. An otorhinolaryngological examination showed that the vocal cords adducted to 45° only, probably secondary to intubation. She went home after four and a half weeks in hospital, taking propylthiouracil 100 mg three times a day and being provided with a salbutamol inhaler; on discharge her serum thyroxine concentration was 70 nmol/l (5·4 μg/100 ml) and her asthma remained well controlled. One week later she was well and had maintained progress; cerebration was still slow and an electroencephalograph showed that there had been considerable improvement, though some abnormality was still present.

Comment

Initially we thought that this thyrotoxic woman had suffered an acute asthmatic attack which had been precipitated by a beta blocker and had resulted in respiratory arrest and anoxic brain damage. Nevertheless, such a pathogenesis is open to discussion and the sequence of events could be explained by her underlying thyrotoxicosis. The acute attack occurred five days after starting propranolol and was sudden, after only a short period of dyspnoea. While propranolol is the most likely explanation for the precipitation of this severe asthmatic attack, it is strange that it was delayed for five days, since the drug's half life is less than six hours—in other words, steady state blood concentrations would have been reached 24 hours later. Conversely, however, the pharmacological half life of propranolol is different from its biological half life, being a few days. This may account for the delay in the onset of our patient's asthmatic attack.

In the past five years there have been reports of an association between the onset of thyrotoxicosis and exacerbation of existing asthma.[1] There is also a relation between the treatment of hypothyroidism and asthma.[2] A retrospective cohort mortality study on 3696 women treated for thyrotoxicosis at the Mayo Clinic from 1946 to 1964 showed that asthma was an underlying cause of death in seven compared with 2·6 expected deaths

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in the normal population.[3] In five of these deaths the onset of thyrotoxicosis had exacerbated features of pre-existing asthma. Other workers have reported a case of an initially well controlled asthmatic woman who deteriorated and shortly after was shown to be thyrotoxic. She was treated with radioiodine but also required carbimazole. Treatment was stopped after a year, but her asthma deteriorated later, when again she was found to be thyrotoxic. Further treatment with radioiodine rendered her euthyroid with improvement in her asthma.[1]

Thus asthmatic patients may spontaneously relapse if they coincidentally develop thyrotoxicosis. The explanations for this are conflicting. In asthma the reduced beta adrenergic responsiveness and fewer beta receptors ("down regulation" of beta adrenoreceptors) may underlie the bronchoconstriction. Some features of thyrotoxicosis resemble the effects of beta adrenergic stimulation, though there is no increase in circulating catecholamine concentrations; possibly there may be more beta receptors or their affinity may be increased ("up regulation" of beta adrenoreceptors).[4] Others have suggested that there is down regulation of beta adrenoreceptors in thyrotoxicosis, with consequent bronchoconstriction. In rats given thyroid hormone an increased density of beta receptors has been reported,[5] but in man there is no firm evidence that the number of beta receptors is changed in thyroid disease.[6]

Rats made hyperthyroid with thyroxine have a reduced pulmonary breakdown of the prostaglandins PGE_2 and $PGF_{2\alpha}$, which are bronchoconstrictors.[7] Hence possibly the wheeze induced by thyroid stimulation may be mediated by prostaglandins.

That our patient had asthma had been suspected by her doctor for a short time; she had a history of eczema. We believe that the beta blockade and the onset of thyrotoxicosis precipitated her first severe asthmatic attack. An asthmatic who becomes thyrotoxic should be closely monitored for any deterioration of the asthma. Asthma may be very mild and hard to diagnose, but however long ago the last asthmatic attack occurred, however mild or infrequent the attacks, or whenever the diagnosis is suspected, beta blockers should be used only with great caution.

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Reading for Pleasure

"Cancer Ward" and modern medicine

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Cancer Ward, Alexander Solzhenitsyn's great novel, was smuggled out from the Soviet Union and published in London in a Russian edition, followed by an English edition in 1968-9. It spread through the world almost instantaneously, being translated into numerous languages and leading directly to a Nobel prize in literature in 1970—"for the ethical force with which he has pursued the indispensable traditions of Russian literature."

Is *Cancer Ward* worth reading today? Of course it is—as an excellent example of the traditional Russian novel at its best with a rich and varied cast. But there is another, non-literary aspect that makes the book worthwhile reading for everybody in the medical profession and, not least, for medical administrators and policy makers. Though "in Time and Space remote," to quote Anthony Powell, the book has much to teach us about the practice of medicine and the organisation of medical care. No comparisons should be made between the material side of medical care in the Soviet Union and the Western world. The East in general has a very primitive standard of hospitals that should be related to equally primitive living conditions. I found hospital environments in Moscow in 1978 to a large extent still on the low level apparent from *Cancer Ward*. No, it is the attitudes in medical care that are of interest.

The story of *Cancer Ward* is simple and easily told. Oleg Kostoglotov, the alter ego of the author, arrives in the mid-1950s at a cancer hospital in a city in a distant Soviet republic. It is not Russia—Oleg mentions explicitly that "The way to Russia was forbidden to him!" He is a deported prisoner, who as an additional burden has developed a malignant tumour. He is admitted to the cancer ward and it is within the four walls of that ward that the whole story takes place—its concentration in time and space is classical. We are shown the medical system, we meet doctors and nurses and learn about their problems, and above all, we follow a group of patients and their struggle—successful or in vain—against the devastating malignant disease that each of them carries.

The humiliating situation in which any patient finds himself, when, suddenly struck down by disease in the midst of active life, he finds himself lying supine in a hospital bed, looking up into unknown and menacing surroundings, is described in a way that reflects personal experience: "In a matter of hours, he had as good as lost all his personal status, reputation and plans for the future—and had turned into eleven stones of hot, white

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