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Management of thyrotoxic crisis

A. MIGNECO, V. OJETTI, A. TESTA, A. DE LORENZO*, N. GENTILONI SILVERI

Department of Emergency Medicine, Catholic University - Rome (Italy)
*Department of Human Nutrition, University of Tor Vergata - Rome (Italy)

Abstract. – The thyrotoxic crisis is a medical emergency caused by an exacerbation of the hyperthyroid state characterized by decompensation of one or more organ systems. Early recognition and aggressive treatment are fundamental in limiting the morbidity and mortality associated with this condition. The crisis has an abrupt onset, and is evoked by a precipitating factor such as infectious diseases, ketoacidosis, acute trauma, thyroidal surgery, 131-I radio-metabolic treatment, administration of iodine-containing materials (amiodarone), parturition. The clinical picture is characterized by four main features: fever, tachycardia or supraventricular arrhythmias, central nervous system symptoms and finally gastrointestinal symptoms. The diagnosis of thyrotoxic crises is often made on the basis of clinical findings alone, since it is difficult in most emergency departments to obtain rapid confirmatory laboratory or nuclear medicine tests. The ultrasound thyroid scan, if available in the emergency room, may suggest an hyperthyroid state showing typical images of Basedow's disease or nodular goiter with their characteristic color-Doppler pattern of hyperactivity, easily distinguishable from a normal gland. The principles of thyroid storm treatments are: reduction of circulating TH's levels; inhibition of the peripheral effects of circulating thyroid hormones (TH); supportive care, in order to reverse systemic decompensation and treatment of the underlying precipitating event.

Key Words:
Thyrotoxicosis, Thyroid storm, Emergency, Management, Therapy.

Introduction

The thyrotoxic crisis, or thyroid storm, is a life threatening exacerbation of the hyperthyroid state characterized by decompensation of one or more organ systems[1]. Usually it complicates Graves disease, but sometimes it occurs in association with toxic nodular goiter. There is no clear cut off value of circulating thyroid hormones (TH) defining the thyroid storm, since the results of laboratory tests show, in most cases, similar serum levels of TH to those observed in uncomplicated thyrotoxicosis[2]. Nevertheless, the rapid recognition of the thyrotoxic crisis and the institution of immediate drug therapy is important in limiting the morbidity and mortality associated with this condition[3,4]. It is difficult to estimate the exact prevalence of thyroid storm, but it may account for <1-2% of hospital admissions for thyrotoxicosis[5]. The mortality of this condition is still high, ranging from 20 to 30%[1].

Pathogenesis

The thyrotoxic crisis typically occurs in patients in whom preexisting hyperthyroidism has not been diagnosed or has been treated insufficiently. The crisis has an abrupt onset, and is almost always evoked by a precipitating factor. How such precipitating events result in an accentuation of thyrotoxicosis is unclear. A further increase of circulating TH's levels or an increased receptor occupancy have been advocated[2]. As there are no TH's serum levels above which thyroid storm inevitably occurs, it is possible that the magnitude and the steepness of the hormone increase may be more important than the absolute values of circulating TH's levels[1,6]. Other possible mechanisms explaining the progression from uncomplicated thyrotoxicosis to thyroid storm include an increase of tissue iodothyronine levels or an enhancement of the cellular response to TH.

Many symptoms and signs of the thyrotoxic crisis result from a concomitant sympathoadrenal hyperactivity, although the con-

centrations of catecholamines in both plasma and urine are normal or even low in hyperthyroidism[7]. However, it is known that TH increase cellular adrenoceptor expression or modify postreceptor pathways leading to a tissue hypersensitivity to catecholamines[8,9].

Possible precipitating events are infectious diseases, ketoacidosis, acute trauma, vigorous palpation of the thyroid gland, thyroidal surgery, 131-I radio-metabolic treatment, administration of iodine-containing materials (iodinated contrast dyes, amiodarone), parturition, toxemia of pregnancy, withdrawal of antithyroid medication, cerebrovascular accidents, pulmonary embolism, acute heart failure and hypoglicemia[2]. Rarely, no precipitating event is detectable.

Clinical presentation and diagnosis

The clinical picture of the thyroid storm is characterized by four main features: (1) fever[10,11], (2) sinus tachycardia or a variety of supraventricular arrhythmias (paroxysmal atrial tachycardia, atrial flutter and atrial fibrillation), often accompanied by various degrees of congestive heart failure[7,12], (3) central nervous system symptoms (agitation, restlessness, confusion, delirium and coma)[13-15], and finally (4) gastrointestinal symptoms, in particular vomiting, diarrhea, intestinal obstruction[16,17]. Unexplained jaundice is suggestive for thyroid storm, but is a poor prognostic sign[3,18]. Dehydration with electrolytes imbalance is another frequent feature. Other typical symptoms and signs of thyrotoxicosis may complete the clinical presentation (goiter, ophtalmopathy, tremor, hyperreflexia, Plummer's nail, systolic hypertension). Younger patients often present sympathetic related symptoms, while older one frequently show cardiovascular dysfunctions[19]. Atypical presentations, such as normothermic crisis, hepatic failure or apathetic storm (extreme weakness) have been reported[20].

Thyroid storm is not an entity distinct from thyrotoxicosis, but rather one end of a spectrum of severity of hyperthyoridism. Burch and Wartofsky's scoring system (Table I) is helpful in distinguishing thyroid storm, "impending" storm and uncomplicated thyrotoxicosis[21]. Nevertheless, the distinction between severe but compensated thyrotoxicosis complicated by other serious diseases (pulmonary embolism, toxemia, acute heart failure) and thyroid storm precipitated by these diseases is not possible. The differentiation between

Table I. Burch and Wartofsky's scoring system

Parameters	Scoring system
Thermoregulatory dysfunction	
Oral temperature (°F)	
99-99.9	5
100-100.9	10
101-101.9	15
102-102.9	20
103-103.9	25
104	30
Cardiovascular dysfunction	
Tachycardia	
90-109	5
110-119	10
120-129	15
130-139	20
>140	25
Congestive heart failure	
Absent	0
Mild (*pedal edema*)	5
Moderate (*bibasal rales*)	10
Severe (*pulmonary oedema*)	15
Atrial fibrillation	
Absent	0
Present	10
Central nervous system symptoms	
Absent	0
Mild agitation	10
Moderate (*Delirium, psychosis, extreme lethargy*)	20
Severe (*Seizure, coma*)	30
Gastrointestinal /hepatic dysfunction	
Absent	0
Moderate (*Diarrhea, nausea, vomiting, abdominal pain*)	10
Severe (*Unexplained jaundice*)	20
Precipitating event	
Absent	0
Present	10

A cumulative score system of 45 or more is highly suggestive of thyroid storm; 25-44 is suggestive of "impending" storm and a score below 25 is unlikely to represent thyroid storm. Modified from *Burch HB, Wartofsky L. Life treating thyrotoxicosis. Endocrinol Metab Clin North Amer 1993; 22: 263-277.*

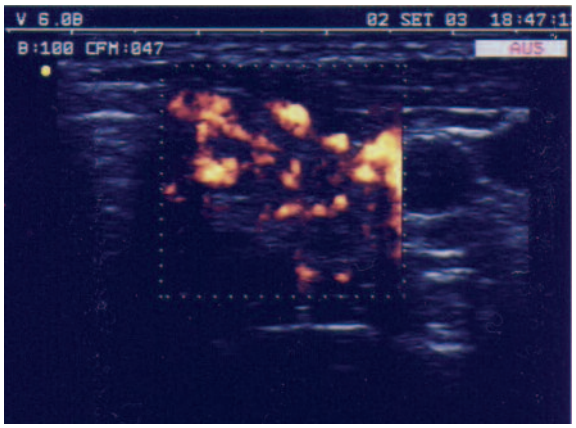

Figure 1. Graves' disease: the transverse sonogram of the left lobe shows diffusely enlarged, heterogeneous and hypoechoic parenchyma (like the near neck muscles); the power-Doppler study demonstrates a typical hypervascular pattern referred to as the *"thyroid inferno"*.

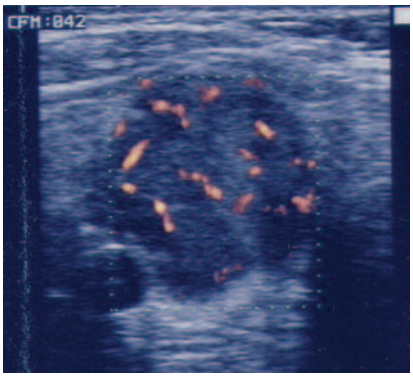

Figure 2. Toxic nodular goiter: the transverse sonogram of the right lobe shows a large solid hypoechoic mass exhibiting rich blood supply internally located on power-Doppler image.

these alternatives is, however, not important because the treatment of these two conditions is the same.

Since it is difficult in most emergency departments to obtain rapid confirmatory laboratory or nuclear medicine tests, the diagnosis of thyrotoxic crises is often made on the basis of clinical findings alone, even if the symptoms and signs may not be specific. Furthermore, low levels of thyroid stimulating hormone (TSH) and high levels of free triiodothyronine (T_3) and free L-thyroxine (T_4) are characteristic, but as yet stated, not helpful in distinguishing uncomplicated thyrotoxicosis from thyroid storm. Other possible laboratory findings (hyperglicemia, hypercalcemia, hypocolesterolemia, hypokaliemia, leukocytosis and liver function abnormalities) are not specific[2,22].

The ultrasound thyroid scan, if available in the emergency room, may suggest an hyperthyroid state showing typical images of Basedow's disease or nodular goiter with their characteristic color-Doppler pattern of hyperactivity (Figures 1 and 2), easily distinguishable from a normal gland (Figure 3).

The diagnostic steps should include: (1) diagnosis of thyrotoxicosis (history of previous hyperthyroidism, clinical features of thyroxicosis and, if available, rapid TH's determination and/or thyroid ultrasound scan); (2) diagnosis of thyroid storm (organ decompensation, Burch and Wartofsky's scoring system); (3) individuation of the precipitating event.

Management

Since the mortality of the thyrotoxic crisis is high, and the confirmation of the diagnosis may be difficult or delayed, treatment should be initiated once thyroid storm is suspected on clinical grounds[23].

Patients should be admitted in the Intensive Unit Care.

The principles of thyroid storm treatments are: (1) lower circulating TH's levels; (2) block peripheral effects of circulating TH; (3)

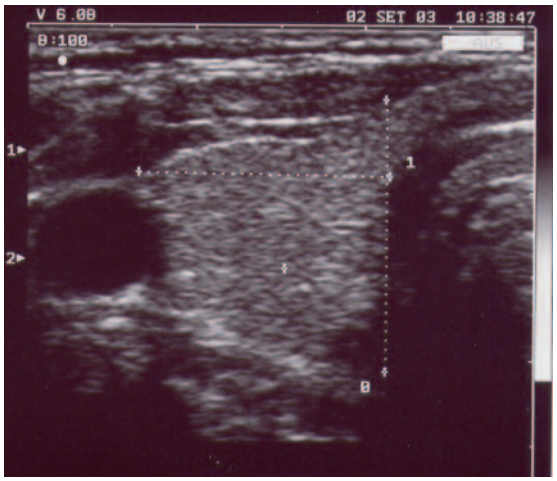

Figure 3. Normal thyroid gland: the transverse sonogram of the right lobe made with high resolution (10 MHz) small parts transducer shows a triangular shape and an homogeneous parenchyma having more echogenicity on respect to the near neck muscles (sternothyroid, sternohyoid, omohyoid and sternocleidomastoid muscles). Tracheal air shadow is clearly identified on the right and the common carotid artery on the left.

supportive care, in order to reverse systemic decompensation; (4) treatment of the underlying precipitating event.

Lowering circulating TH's levels is achieved either preventing TH's synthesis or blocking TH's release. Both propylthiouracil (PTU) and methimazole (MMI) inhibit the synthesis of new TH interfering with the iodide oxidation and organification process[23]. The recommended dose for PTU are 200-250 every 6 hours and for MMI 20-25 mg every 6 hours whether orally, via nasogastric tube or through rectal administration[18]. The effect is delayed in 3-4 days.

Inorganic iodine preparations block the TH's release by inhibiting thyroglobulin protheolysis (Wolff-Chaikof effect)[23]. The iodine therapy must be administered after successful inhibition of new TH's synthesis is achieved (2-3 h after PTU or MMI administration) since the use of iodine alone would lead to enhance intraglandular TH's stores[24] and possible worsening of the thyrotoxic crisis (escape phenomenon). Iopanoic acid and ipodate are given at an initial dose of 2 g i.v. followed by 1 g daily[25]. Renal impairment and dehydration are contraindications, while hepatopatic patients should be carefully monitored for liver functional tests since iopanoic acid is concentrated in the liver.

Other iodine containing compounds are Lugol's solution (10 drops every 3h) and saturated solution of potassium iodide (8 drops every 6h)[23]. In patients allergic to iodine, Lithium (300 mg every 6h) can be used as alternative agent, since it impairs TH's release.

Another way to lower circulating TH's levels is the administration of high doses of cholestyramin. This drug binds the TH in the gastrointestinal tract inhibiting their enterohepatic circulation[26].

Other methods to remove the excessive amount of circulating TH are peritoneal dyalisis, plasmapheresis or hemoperfusion through resin or charcoal[27,28].

Inhibition of TH peripheral action is achieved administering antiadrenergic drugs and blocking the peripheral T_4 to T_3 conversion. Inhibition of T_4 to T_3 conversion decreases the overall TH's peripheral activity, since T_3 is more potent than T_4, and 80% of T_3 production occurs peripherally through T_4 monodeiodation.

Glucocorticoids[21], iopanoic acid, ipodate[18] and PTU[23] all sinergically inhibit peripheral T4 to T3 conversion. Desametasone, 2 mg i.v. every 6 hours, or hydrocortisone 300 mg i.v. and then 100 mg i.v. every 8 hours are recommended regimens. Additional beneficial actions of glucocorticoid therapy are the correction of the relative adrenal insufficiency, present in some cases of thyroid storm, and the inhibition of TH's release, when given at high doses[2].

Beta adrenergic blockers are first choice therapy for the management of the concomitant sympathoadrenal activation. Heart rate control, reduction of cardiac output and workload contribute to lessen the cardiovascular symptoms and signs of the thyrotoxic crisis[5].

Propranolol in a dose of 80-120 mg every 6 hours orally, or 1 mg i.v. followed by 2-3 mg every 3 hours is the most widely used β-blocker in cases of thyroid storm[1,29,30]. Propranolol also inhibits T4 monodeiodation, and has beneficial effects on the associated fever and agitation[2]. More recently esmolol, a short acting β-blocker, at a loading dose of 250-500 μg/kg/min and successively as continuous infusion of 50-100 μg/kg/min, has been successfully used[31].

β-blockers are contraindicated in presence of severe heart failure cardiac and shock. The most important issue in thyrotoxic heart failure is the contribution of accelerated heart rate. If the tachycardia is thought to be the main cause of the heart failure, then a trial of β-adrenoceptor blockade is reasonable, despite the negative inotropic effect with possibility of depressing myocardial contractility. If the cardiac failure is due to an underlying ischaemic, hypertensive or valvular heart disease, then β-blockers are probably best avoided, and digoxin, diuretics or inotropic agents should be initiated[32].

Since clinical situations are often ambiguous, a short acting β-adrenoceptor blocker like esmolol should be initiated. If there is evidence of worsening of the congestive failure or hypotension the drug can be promptly withdrawn[33].

Treatments for systemic decompensation are aggressive fluid repletion with saline solutions containing dextrose to replace glycogen hepatic stores (up to 3-5 liters daily)[21], electrolyte replacement, acetaminophen administration and, if needed, peripheral cooling as antipyretic agents. Salicylates should be

avoided, because they compete with TH for binding to serum proteins and therefore increase free hormone serum concentrations[34]. Fluid repletion should be undertaken cautiously if heart failure occurs.

Supraventricular arrhythmias should be managed with current antiarrhythmic therapy (adenosine, overdrive pacing) if not responsive to β-adrenergic blockade. Treatment of congestive heart failure has been yet discussed. Anticoagulation therapy should be started promptly, especially if atrial fibrillation occurs[35]. Hyperactive patients require sedation, and oxygen should be administered if needed.

Treatments for the precipitating event include administration of antibiotics if an infection source can be identified and the management of concomitant ketoacidosis, toxemia or hypoglicemia.

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