Fever after ICU discharge

Toxicology case presentation

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History

- M/59
- Known case of depressive disorder and FU by Psy
- Hx of antipsychotic induced EPS required medications adjustment
- Usual medication:
  - benzhexol (artane) 2mg bd
  - clonazepam 1mg nocte
  - fluoxetine 80mg nocte
  - lorazepam 0.5mg bd
  - risperidone 1mg nocte
  - inderal 20mg bd

History

- Admited initially to medical ward for delusional idea
- denied visual / auditory hallucination
- Good drug compliance
- P/E:
  - mask face and resting tremor over RUL
  - Cogwheel rigidity mainly over bilateral UL
- CT brain: no SOL / hemorrhage
- Electrolytes and CK normal
- => Imp: extra-pyramidal S/E of anti-psychotic drugs

History

- Psy consultation
- Medication modification:
  - benzhexol (artane) 2mg bd
  - clonazepam 1mg nocte -> 0.5mg nocte
  - fluoxetine 80mg nocte -> 70mg nocte
  - lorazepam 0.5mg bd
  - risperidone 1mg nocte
  - inderal 20mg bd

History

- Found to have URI symptom
- CXR clear
- Put on Augmentin
- To TWEH for rehab
- RT inserted for feeding in view of risk of aspiration
- Developed desaturation and fever
- Worry about HAP and transferred back to PYNEH for further Mx

History

- GCS drop from 15/15 to 10/15
- Increase tone over Rt side
- intubated for airway protection
- CT brain repeated unremarkable
- To ICU x further Mx
- All antipsychotic stopped
- Worry about aspiration pneumonia and antibiotic upgraded to tazocin
- CXR clear
- Extubated on next day
- GCS back to normal spontaneously
- Fever down (37.5C)
- D/c from ICU after one day of stay

History

- In medical ward: assessed by psy and worry about EPS of risperidone,
- Risperidone was stopped and fluoxetine was reduced to 20mg daily
- Two days afterward: fever 38.2C, confused speech, SBP 170-190 (usual SBP around 120-160), HR 120
- LP showed normal glucose/ protein/ smear/ WCC
- Further drop of GCS on following day to E4V2M4, temp 39, antibiotic changed from timentin to tazocin, desaturation required high flow O2, CXR clear
- -> ICU consulted for support

History

- On assessment:
  - GCS 6/15
  - BP 130/80, HR 130, temp 41C, SpO2 98% in 15L O2
  - Sweaty, agitated, tone increase over limbs, clonus +ve
  - Dilated pupil with sluggish response to light
- To ICU and intubated

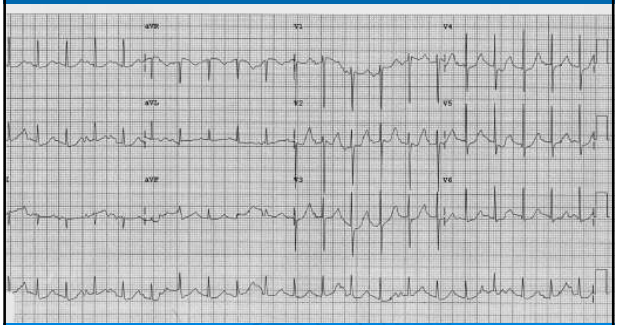
Any comments on DDx

- Serotonin syndrome (SS)
- Neuroleptic malignant syndrome (NMS)
- Sympathomimetic overdose
- ….

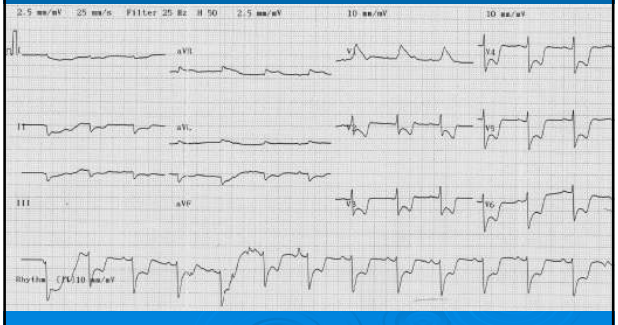
Progress in ICU

- Developed cardiac arrest soon after intubation in ICU

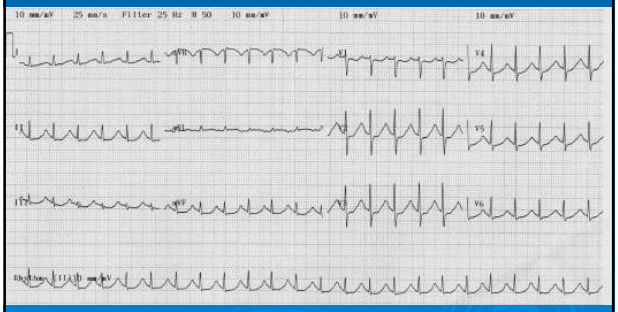
ECG before ICU admission



ECG on ICU admission



ECG after ROSC



Progress in ICU

- CPR last for 9min with ROSC
- Required high dose noradrenaline for BP support
- Given around 2.5L fluid challenge

Progress in ICU

- pH 7.359, PCO2 3.69, PO2 27.3, HCO3 15.3, BE -8.5
- Na 154, K 3.5, Ur 16.8, Cr 255 (baseline normal)
- WCC 18.9, Hb 14.6, PLT 339, INR 1.4, APTT 36
- CPK 2218, TnI 3.13, LDH 1086, Ca 2.22, PO4 1.32

Progress

- Midazolam + morphine infusion given
- Able to decrease NA slowly on initial 5hr after ICU admission
- Developed rapid of BP despite high dose Norad and fluid challenge
- Temp upto 42C
- Echo by cardiac showed hyperdynamic heart, no RWMA
- Developed cardiac arrest again around 11hr after ICU admission and failed CPR

Any comments ?

Drug induced hyperthermia

Body temperature regulation

- Hyperthermia occurs when metabolic heat production exceeds heat dissipation
- Temperature regulation is divided into
  - Obligatory thermogenesis -> metabolic processes contributes to maintaining a constant body temperature
  - Adaptive thermogenesis -> acts in response to acute changes in environmental temperatures
- Governed through hypothalamic regulation of the sympathetic nervous system and mitochondrial oxidative phosphorylation
- Norepinephrine, dopamine, and serotonin played an important role

Body temperature regulation

- Sympathetic nervous system activation contributes to effects on thermogenesis by
  - cutaneous vasoconstriction
  - nonshivering thermogenesis
- Nonshivering thermogenesis occurs primarily by uncoupling of oxidative phosphorylation through the activity of a group of mitochondrial proteins known as uncoupling proteins (UCP)

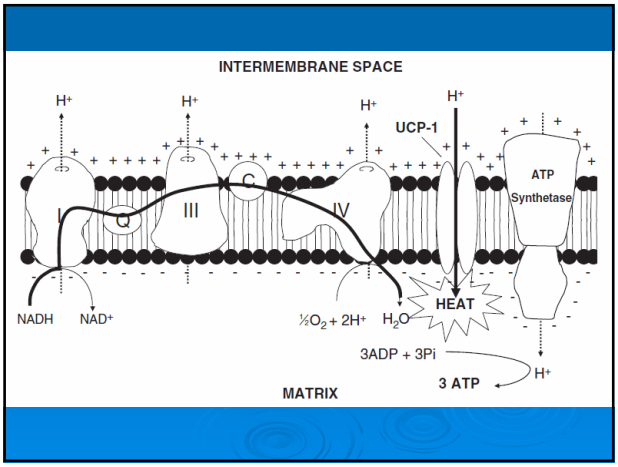


Table 1. Hyperthermic syndromes and their causative agents

Hyperthermic syndrome	Causative drugs	
Malignant hyperthermia	**Anesthetic gases:** halothane, ethflaurage, isoflurane, methoxyflurane, cyclopropane, diethyl ether, ethylene **Muscle relaxers:** succinylcholine, decamethonium, gallamine	
Neuroleptic malignant syndrome	**Neuroleptics:** phenothiazines, butyrophenones, thioxanthenes **Tricyclic antidepressants** **Monoamine oxidase inhibitors** **Anticonvulsants** **Benzodiazepines**	
Anticholinergic poisoning	Antihistamines	Glycopyrrolate
	Atropine	Hydroxyzine
	Belladonna alkaloids	Hyoscyamine
	Benztropine	Meclizine
	Carbamazepine	Orphenadrine
	Chlorpheniramine	Phenothiazines
	Clozapine	Procainamide
	Diphenhydramine	Quinidine
	Doxylamine	Quinine
	Disopyramide	Tricyclic antidepressants
	Glutethimide	
Sympathomimetic poisoning	Cocaine	
	Ecstasy	
	Amphetamines	
	Methamphetamines	
Serotonin syndrome	L-tryptophan	Tricyclic antidepressants
	Amphetamine	Meperidine
	Cocaine	Dexotromethorphan
	Ecstasy	Monamine oxidase inhibitors
	Fenfluramine	
	Mescaline	
	Psilocin	
	L-dopa/carbidopa	
	Lithium	
	Lysergic acid diethylamide	
	Selective serotonin reuptake inhibitors	
	Serotonin reuptake inhibitors	

Malignant hyperthermia

- Genetic disorder of skeletal muscle metabolism
- dysfunctional calcium channels reside in the sarcoplasmic reticulum and permit an uncontrolled influxof calcium into the cell
- leads to increased production of adenosine triphosphate in the mitochondria, which results in muscle contraction, accelerated muscle metabolism, and uncoupling of the oxidative phosphorylation
- Metabolic rates may increase to 500% of baseline

Malignant hyperthermia

- Early signs: tachycardia, tachypnea, muscle rigidity, ventricular dysrythmias, and hypercarbia
- Late findings include hyperthermia, sweating, skin mottling, mydriasis, myoglobinuria, mixed metabolic and respiratory acidosis, rhabdomyolysis, hyperkalemia, renal/ liver/ heart failure and DIC

Neuroleptic malignant syndrome

- Extrapyramidal syndrome associated with the use of antipsychotic drugs or with the withdrawal of dopaminergic agents
- Alter hypothalamic regulation through elevated serotonin or decreased dopamine in CNS

Neuroleptic malignant syndrome

- Diagnostic criteria
  - exposure to an inciting agent within 7 days of symptom onset
  - hyperthermia with temp >=38C
  - muscle rigidity
  - exclusion of any other drug-related or systemic illness
  - five of the following
    - altered mental status, tachycardia, hypertension or hypotension, tachypnea or hypoxia, diaphoresis or sialorrhea, tremor, incontinence, elevated creatinine phosphokinase or myoglobinuria, leukocytosis, or metabolic acidosis

Anticholinergics poisoning

- Hyperthermia is caused by both central and peripheral muscarinic receptor blockade
- Central blockade -> altered mental status, confusion, agitation, restlessness, seizures, and coma
- Peripheral blockade -> impaired sweating, dry mouth and axillae, mydriasis, tachycardia, flushing, urinary retention, and decreased bowel sounds
- Children are more likely than adults to develop hyperthermia

Sympathomimetics poisoning

- increasing concentrations of norepinephrine, dopamine, and serotonin in the CNS
- Causing vasoconstriction, increase muscle activity through agitation, seizures, and/or rigidity, increased hepatic metabolism

Serotonin syndrome

- Characterized by cognitive/behavioral (confusion,agitation), autonomic (tachycardia, hyper- or hypotension, mydriasis), and neuromuscular abnormalities (clonus, hyperreflexia, tremor)
- Heat is produced as a byproduct of agitation, tremor, and muscle rigidity.
- Hyperthermia is an inconsistent finding and only present in about 50% of cases

Table 2: Most frequent distinctions between serotonin syndrome and neuroleptic malignant syndrome[2,3,8–10,17–20]

Characteristic	Serotonin syndrome	NMS
Onset	Sudden, within 24 h following introduction of a serotonergic agent	Slower, within 7 d following introduction of a neuroleptic agent
Symptoms	Agitation, diarrhea	Dysphagia, hypersalivation, incontinence
Signs	Dilated pupils, myoclonus, hyperreflexia	Hyperthermia (> 38°C), akinesia, extrapyramidal "lead pipe" rigidity, rhabdomyolysis
Mortality	23 deaths reported until 1999*	15%–20%

Note: NMS = neuroleptic malignant syndrome.
*No percentage is reported in the literature, because there are too few cases.

Table 2. Therapy for drug-induced hyperthermia

Discontinuation of offending agent
Stop excess heat production (agitation, seizures, shivering); sedation, paralysis if needed
Volume replacement
External cooling
Dantrolene (malignant hyperthermia, neuroleptic malignant syndrome)
Bromocriptine (neuroleptic malignant syndrome)
Physostigmine (anticholinergic poisoning)
Cyproheptadine (serotonin syndrome)