#### Joint Clinical Meeting and Didactic Lecture RHTSK AED AUGUST 2009

### CKC

- \* M/30+
- Good past health
- \* BP 128/67 P92 GCS 15/15
- Presented to AED due to progressive generalized muscle weakness shortly after exercise
- Unable to stand up
- Similar episodes in the past but spontaneously subsided
- \* No LOC/ injury/ neck or back pain/ fever

What are the DDx in your mind?(patient with 4 limbs paralysis)

# DDx

- Differential Diagnosis
- Spinal cord
  - Space-occupying lesion such as hematoma and malignancies
  - Transverse myelitis
  - Infection (rabies, tetanus)
- Nerve
  - Food poisoning (e.g. shellfish poisoning, tetrodotoxin poisoning)
  - Tick paralysis
  - Guillain-Barre Syndrome

# DDx

#### Neuromuscular junction

- Myansthenia Gravis/ Eaton Lambert Syndrome
- Infection (e.g. Botulism)
- Neuromuscular blocking agents (e.g. organophosphate)
- Muscle
  - Myositis
  - Periodic paralysis
  - Electrolyte disturbance
  - Muscular dystrophy

On physical examination , what sort of thing you would look for ?

- General condition of the patient
- Neurological examination
- \* CVS
- Skin lesion

- \* BP 128/67 P 92
- **\*** GCS 15/15
- Dehydrated
- Strong body build



- All 4 limbs power grade 1/5; cranial nerve intact; sensation normal; anal tone strong
- no cerebellar sign
- Other neurological examination was normal
- Chest/CVS/abdomen unremarkable
- Clinically euthyroid
- No local muscle tenderness

# DDx

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## DDx

#### Neuromuscular junction

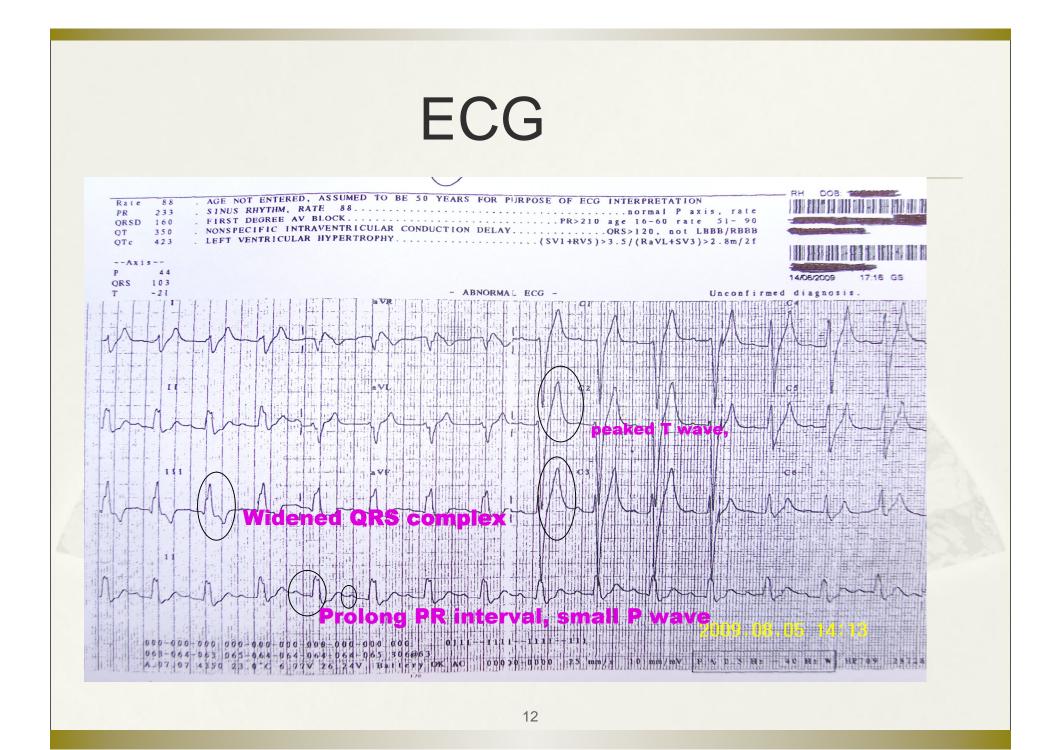
Myansthenia Gravis/ Eaton Lambert Syndrome

(e.g.

- Infection (e.g. Botulism)
- Neuromuscular blocking agents organophosphate)
- Muscle
  - Myositis
  - Periodic paralysis
  - Electrolyte disturbance
  - Muscular dystrophy

### What bedside Ix you want to do?

\* H'stix
\* ECG
\* Blood for L/RFT
\* ABG
\* CXR, AXR
\* Urine multistix



### Ix: Blood test

- **\*** H'stix 5.2
- \* Na 129
- **\*** K 8.6
- **\*** Urea 13.2
- Creatinine 233



- **\*** CK 1632; troponin level normal
- \* Hb 16.6
- Calcium 2.21 (adjusted)

### Ix: Blood test

#### ABG:

- \* pH 7.35
- \* p02 15.88
- \* pCO2 3.9
- \* HCO3 16.1
- \* BE -7.7
- \* 02 saturation 98.2
- \* What is the acid-base pattern?
- Metabolic acidosis with respiratory compensation

# Other useful investigations available at AED?\* USG

- X-ray (spine, KUB)
- Urine test (myoglobulin/ toxicology)
- \* TFT, chloride, lactate, serum osmolarity

#### Conclusion

Hyperkalemia
Renal impairment
with metabolic acidosis
Body builder

Any further history?? Drug history!!



# **Drug History**



- Body builder attending body building competition
- Told by friends and seniors that high dose potassium supplements are good for counteracting hypokalemic effect of diuretics and can "saturate the renal tubule" to reduce tubular resorption of sodium thus reducing the water retention
- \* So.....

# **Drug History**

- Starting from 1 week prior to competition, he took 30-40 tablets of slow K (600mg each tablet) EVERYDAY
- Lasix 40mg daily in the 3 days for diuresis prior to competition
- Symptom onset shortly after finishing competition



# Progress (1)

- Patient was managed in R room with cardiac monitor
- IV fluid replacement, calcium chloride and dextrose-insulin drip were started in AED
- Muscle power gradually improved in AED shortly after IV fluid
- Subsequently transferred to ICU

# Progress (2)

- IVF, dextrose-insulin drip and close monitoring were continued in ICU
- **\*** Resonium was also started.
- Electrolyte derangement, acid-base imbalance and renal function gradually improved.
- Serum creatinine kinase level gradually decreased with IVF replacement. Serum troponin and urine myoglobulin were all along negative
- USG kidney was normal

#### Admitted polypharmacy for body building

- \* Protein supplements such as creatine
- Anabolic steroids such as Stanozolol and testosterone
- \* Others
  - \* Tamoxifen
  - \* Anastrozole
  - \* Vitamins
  - \* Topical oils



#### Urine toxicology result (by TRL)

- \* Frusemide
- \* Spironolactone metabolite
- Paracetamol
- \* Diphenhydramine
- Dimenhydrinate
- Bisacodyl metabolite
- \* Quinine
- No corticosteroid found on target analysis (However, the detection of anabolic analysis was not included in the assay)
- Finally discharged on Day 4

#### It is not the isolated case

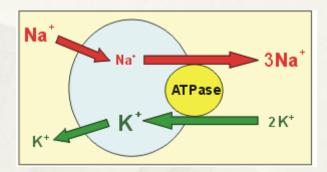
- We also encountered another body builder with the same presentation on the same day
- \* With a fatal case one year before

 Is it common problem and what is the risk factor in this group of people (body builder)?

## Potassium in body builder

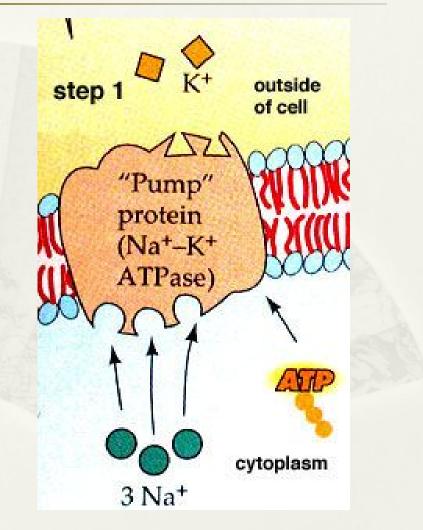
- Body builders believe that potassium
- can improve the muscle power for daily training=→ to build up the muscle
- It should be noted that in the muscles obtained from K<sup>+</sup>-deficient, the data indicate that K<sup>+</sup> deficiency may lead to severe impairment of contractile performance.
- \* (Na<sup>+</sup>-K<sup>+</sup> Pump Regulation and Skeletal Muscle Contractility *Physiol. Rev.* 83: 1269-1324, 2003)

- Over the last 15 yr, numerous longitudinal and cross-sectional studies have demonstrated that training leads to an upregulation and inactivity to a downregulation of the content of Na<sup>+</sup>-K<sup>+</sup> pumps in skeletal muscle
- there is good evidence that training improves the ability to clear the exerciseinduced increase in plasma K<sup>+</sup>, in part as a result of an upregulation of the content of Na<sup>+</sup>-K<sup>+</sup> pumps in skeletal muscle.
- The content of Na<sup>+</sup>-K<sup>+</sup> pumps in skeletal muscle is correlated to the capacity for energy turnover.
- K<sup>+</sup>-deficient fodder, the Na<sup>+</sup>-K<sup>+</sup> pump content of skeletal muscle underwent a marked decrease of up to 80%



# Na<sup>+</sup>-K<sup>+</sup> pump

- downregulation of Na<sup>+</sup>-K<sup>+</sup> pump capacity in skeletal muscle is an early regulatory adaptation to K<sup>+</sup> deficiency, favoring a net release of K<sup>+</sup> from the large muscular K<sup>+</sup> pool.
- In conclusion, dietary K<sup>+</sup> overload induces the opposite change in the content of Na<sup>+</sup>-K<sup>+</sup> pumps in skeletal muscle to that seen in K<sup>+</sup> deficiency. This upregulation might facilitate and increase physical performance.



# Potassium in body builder

- Replacement for potassium as they use diuretic (lasix)
- They also use spironolactone however the effect is slow
- So before competition, they would use loop diuretic to have a good delineation of vascular and muscle striation under skin

# Slow K

- Each 600mg slow K tablet contains 8mmol
   KCl
- Completely absorbed; 90% renally excreted in the first 8 hours
- Toxic if single ingestion of >2mmol/kg (potassium renal homeostasis overwhelmed)
- Potentially fatal with single ingestion
   >4mmol/kg
- \* Eg. In our pt, he took 320mmol per day
- \* Around 4.6mmol/kg\_per day (if 70kg)

- Mortality after slow K overdose has been reported with unintentional misuse and overdose, even in the presence of normal cardiac and renal function
- Rapidly fatal due to cardiac toxicity of hyperkalemia
- Rarely, rapidly progressive flaccid muscle weakness which may progress to quadriplegia or even respiratory muscle weakness and respiratory failure

 But why our patient or most of the cases had taken slow K for more than a week but only develop symptom shortly after the body building competition

????

- That may be the combination effect of slow
   K, creatine and diuretic
- Normally our kidney is able to manage the excessive potassium level
- \* But in dehydration state??

#### Creatine

 High level of creatine>2g/day is unnecessary and potentially harmaful to the kidney

#### **Diuretic** prior to competition

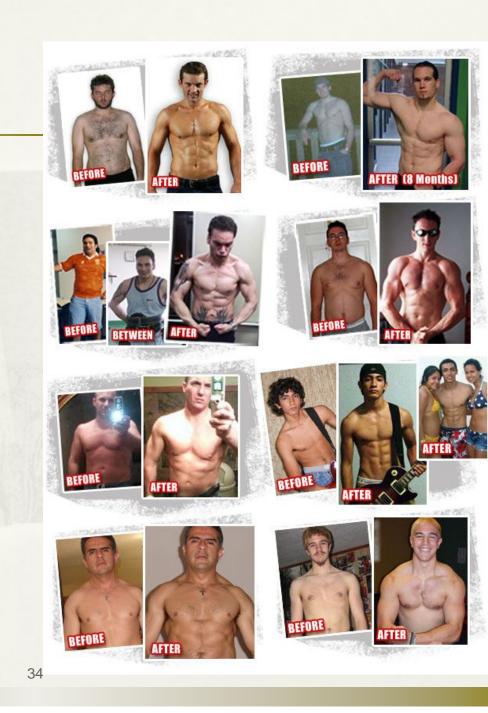
- dehydration (urea 13.2) and worsening of the renal function (creatinine 233)
- ➔ Symptomatic hyperkalamia

# Treatment of hyperkalemia:

- 1. Antagonizes cardiac toxity
  - Calcium chloride
- 2. Potassium intracellarly shift
  - Sodium bicarbonate
  - Insulin-dextrose
  - B agonist inhalation
  - NaHCO3
- 3. Other
  - Loop diurctics
  - Resonium
  - Haemodialysis
- 4. Treat the underlying causes

#### Discussion

#### Ergogenic aids in body builders



### **Body builders**

- Goal of training
  - \* Large muscle size
  - High degree of symmetrical and well defined muscle shape
  - \* Good delineation of vascular outline and muscle striation under skin
- Performance in body building competition judged by appearance instead of physical performance
- Categorised by body weight



### **Body builders**

- Target achieved by retaining huge muscle mass while reducing body fat and water content
  - \* Rigid diet control
  - \* Restriction of dietary salt and fat
  - \* Diuretics
  - \* Drugs to antagonize side effects



# **Body builders**

\* Off season:



- \* Aim to increase muscle mass
- \* In positive energy balance for muscle anabolism
- \* Adequate CHO to bulk up
- Adequate dietary protein to provide aminoacids for protein synthesis
- 3 months prior to competition
  - \* Attempt to retain muscle mass and reduce body fat to very low level

# **Body builders**

- Pre-contest phase
  - In negative energy balance so that body fat can be oxidised
  - Cut CHO
  - Adequate protein intake to maintain muscle mass and as energy source
  - A relatively high protein intake (30% of energy intake) reduces less lean muscle mass when compared with lower protein intake (15% of energy intake)
  - Higher protein intake increases thermogenic effect and reduces body fat
  - \* Renal overload!!

#### **Body builders**

- Prone to renal failure and hyperkalemia
  - \* Dehydration
  - Drugs
  - Renal overload with protein
  - Rhabdomyolysis (exertion, isometric exercise for posing)

#### Case reports

- Myocardia infarction, hyperkalemia and ventricular tachycardia in a young male bodybuilder. *Int J Cardiology 1994; 44: 171-174*
- A bodybuilder with diuretic abuse presenting with symptomatic hypotension and hyperkalemia. *America Journal of Emergency Medicine 1996; 14: 96-98*
- End-stage renal failure in body builder: a multifactorial proces or simply doping? *Nephrol Dial Transplant 2001; 16: 163-165*

# **Ergogenic aids**

- Substances or methods used by athletes to enhance training efficiency and achieve better athletic performance
- Drugs vs supplements
- Evidence-based vs traditional unproven methods (e.g. experience from peers/ seniors)
- Legal vs illegal or banned
- Physicians and other allied health care professionals vs self over-the-counter prescription and illegal drug dealers



FDA Warns Consumers to Stop Using Hydroxycut Products

**News & Events** 

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE May 1, 2009 Media Inquiries: Susan Cruzan, 301-796-

15/06/2009 9:51 PM

4540 Consumer Inguiries: 888-INFO-FDA

#### FDA Warns Consumers to Stop Using Hydroxycut Products Dietary Supplements Linked to One Death; Pose Risk of Liver Injury

The U.S. Food and Drug Administration is warning consumers to immediately stop using Hydroxycut products by Iovate Health Sciences Inc., of Oakville, Ontario and distributed by Iovate Health Sciences USA Inc. of Blasdell, N.Y. Some Hydroxycut products are associated with a number of serious liver injuries. Iovate has agreed to recall Hydroxycut products from the market.

The FDA has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, an indicator of potential liver injury, to liver damage requiring liver transplant. One death due to liver failure has been reported to the FDA. Other health problems reported include seizures; cardiovascular disorders; and rhabdomyolysis, a type of muscle damage that can lead to other serious health problems such as kidney failure.

Liver injury, although rare, was reported by patients at the doses of Hydroxycut recommended on the bottle. Symptoms of liver injury include jaundice (yellowing of the skin or whites of the eyes) and brown urine. Other symptoms include nausea, vomiting, light-colored stools, excessive fatigue, weakness, stomach or abdominal pain, itching, and loss of appetite.

"The FDA urges consumers to discontinue use of Hydroxycut products in order to avoid any undue risk. Adverse events are rare, but exist. Consumers should consult a physician or other health care professional if they are experiencing symptoms possibly associated with these products," said Linda Katz, M.D., interim chief medical officer of the FDA's Center for Food Safety and Applied Nutrition. Hydroxycut products are dietary supplements that are marketed for weight-loss, as fat burners, as energy-enhancers, as low carb diet aids, and for water loss under the Iovate and MuscleTech brand names. The list of products being recalled by Iovate currently includes:

- Hydroxycut Regular Rapid Release Caplets
- Hydroxycut Caffeine-Free Rapid Release Caplets
- Hydroxycut Hardcore Liquid Caplets
- Hydroxycut Max Liquid Caplets
- Hydroxycut Regular Drink Packets

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149575.htm

Page 1 of 2

# **Ergogenic aids**

- Classification
  - \* Physiological
  - \* Psychological
  - \* Nutritional (supplement)
  - \* Pharmacological

- Refers to substances taken to augment the diet
- Most are benign (vitamins, protein and minerals)
- Drugs (e.g. stimulants, steroid precursors) sold as "supplement"
- Mega-doses of supplements
- Effects sometimes unproven
- Supplements taken in overdose may be harmful

- Creatine
  - Most common nutritional supplements
  - \* Effect:



- Enhancement of ATP regeneration, maximizing anaerobic events
- \* Increase muscle mass
- Increase strength and sports performance (variable response)
- Heat-related illness
- Renal dysfunction

 \* "...serum corticol during recovery tends to be higher in creatine group than in placebo..."

(Med. Sci. Sports Exerc 33. (3) 449-453: 2001)

 \* "...resting testosterone concentrations were elevated in creatine group... this study demonstrates the efficacy of creatine on strength performance..."

(Int J Sport Nutr Exerc Metab 16. (4): 430-446. 2006)

 \* "...norepinephrine and dopamine concentration were significantly higher at 24 hour...creatine supplementation had a positive effect on mood state..." (Psychopharmacology 185. 93-103. 2006)

#### Amino acids

- ∗ To counteract the increase use of amino acid during physical exertion → increase strength, endurance and muscle integrity
- \* Usually supplied and administered without medical supervision
- Used for pharmacological purpose rather than nutritional purpose
- Multiple studies showed no effect on physical performance, endurance, muscle strength or aerobic power

- \* Side effects
  - \* GI upset
  - \* Neurological symptom (headache, weakness)
  - \* Brain damage
  - \* Hepatotoxicity
  - \* Secretagogue for hormones like GH, insulin
  - \* Psychosis

#### Caffeine

- Thought to be most beneficial for performance in endurance events
- Effects more pronounced in those not regularly using caffeine
- \* Ergogenic effects supported by meta-analysis
- Case reports of short-term risk of SCD associated with heavy coffee consumption
- \* Usually safe at appropriate dose

- Ephedra
  - \* Active component: ephedrine, pseudoephedrine
  - \* Effect:
    - \* Weight reduction
    - Increased endogenous catecholamines and direct beta-adrenergic effect
    - \* Increase BMR and lipolysis
    - \* Cardiac: MI, cardiomyopathy, vasospasm, arrthymia, decreased serum magnesium → long QT
    - \* CNS: ICH, seizure

- \* Psychosis
- Heat-related illness
- \* Sympathomimetic toxidrome
- Believed to decrease fatigue, increase energy, decrease fat mass and muscle definition
- \* *Majority of literature: no effect on athletic performance*
- \* Banned by FDA and many sports organizations

# **Ergogenic aids**

- Pharmacological aids
  - \* To increase lean mass and muscle strength
    - Anabolic steroids
    - \* Growth hormones
    - \* Ginseng
    - \* Amino-acids
  - \* To increase energy
    - \* Stimulants
  - \* To increase oxygenation
    - Blood doping
    - \* Erythropoietin

# **Ergogenic aids**

- Pharmacological aids
  - \* Others
    - \* Analgesics
    - \* Diuretics
    - \* Anxiolytics

Some agents for antagonizing the unwanted side effects of ergonenic aids

# Doping

In 1997, Sports Illustrated asked 198 US Olympians,

"Would you take a banned performance enhancing substance if you were guaranteed to win and not get caught?"

\* 98% answered "YES"

# Doping

Then, when asked,

"Would you take the same undetectable substance if it would contribute to winning every competition for 5 years, then result in death?"

\* Over 50% still answered "YES!!!"

- Anabolic steroid
  - \* 30% body builders attending competition
  - Usually dosed in supratherapeutic regimen
  - \* Testosterone and Dianabol commonly used
  - Wrine detection difficult
    - Hundreds of different kinds of steroid and their specific metabolites
    - Need to specifically investigate the individual metabolites instead of checking the presence of steroid

- \* Effect:
  - \* Increase muscle mass and strength
  - \* Increase erythropoietin production
  - \* Decrease HD-L
  - \* Aggressive and manic behavior
  - \* Acne
  - \* Hypertension
  - \* Venous thrombosis



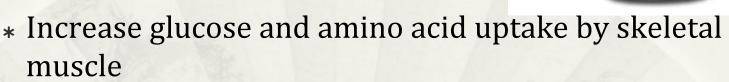
- \* Fluid retention
- \* Muscle cramp
- \* Gynaecomastia
- \* Impotence
- \* Alopecia
- \* Premature closure of growth plates

- Case report of ESRF in body builder using anabolic steroid
  - Postulated to be related to the aromatization properties of certain steroid such as testosterone, or secondary to process such as GN
- Mechanism also related to the development of gynaecomastia
- Counterfeit steroid → case reports of liver and renal toxicity
- \* Overdose  $\rightarrow$  liver toxicity

#### \* Lindstom et al. (1990)

- \* 94% considered anabolic steroid dangerous
- \* 81% anabolic steroid user experienced side effects
  - \* 74% of them continued the steroid usage despite side effects

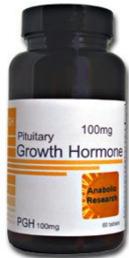
- Human Growth Hormone
  - \* Effect:



- \* Increase protein synthesis
- \* Increase lipid breakdown
- \* Increase rate of bone growth
- \* No studies reported improvement in ex. performance

62

- Acromegaly, Insulin resistance
- \* Myopathy
- Cardiomyopathy



- Erythropoietin
  - \* Effect:
    - \* Increase red cell production
    - Increase hematocrit concentration
    - \* Increase time to exhaustion
    - \* Hyperviscosity syndrome
    - \* Hypertension



#### Diuretics

- \* Diuretic effect more prominent in loop diuretics then in thiazide diuretics
- Direct effect on sports regulated according to body weights e.g. body building
- Banned also for urine dilution which complicates the testing for doping agents in urine

- **\*** Others:
  - Cocaine
  - \* Metamphetamine
  - \* Alcohol
  - \* Marijuana
  - \* Potassium
  - \* Anxiolytics
  - \* Analgesic

- To antagonise side effects:
  - \* Potassium supplements
    - \* For hypokalemia associated with diuretics
  - \* Quinine
    - For muscle cramps (training, anabolic steroid, electrolyte.....)
  - \* Tamoxifen, Anastozole
    - \* For gynaecomastia, fluid retention

# EAT AT YOUR OWN RISK!!

