THE NORTHERN HOSPITAL

CREATINE KINASE - (CK)

"I who am the Sultan of Sultans, Distributor of Crowns to Monarchs over the whole Surface of the Globe, God's Shadow on Earth, Sultan and Padishah of the White Sea and of the Black Sea, of Rumelia and Anatolia, of Karaman and the nations of Rum, Zulcadir, Diyarbekir, Kurdistan, Azerbaijan, Persia, Damascus, Aleppo, Cairo, Mecca, Medina, Jerusalem and all of Arabia, Yemen and many other lands that my noble forebears and illustrious ancestors.... conquered by the force of their arms and that my August Majesty has also conquered with my blazing sword and victorious sabre...."

Letter From Suleiman the Magnificent to King Francis I of France.

Left: Suleiman the Magnificent, oil on canvas, Titian or the school of Titian, c.1530

Right: Personal monogram of Suleiman the Magnificent,

"Mustafa entered, the drama commenced, and he was seized on every side. But the Prince in a moment he believed would be his last, regained his strength and was animated with heroic courage. He knew that if he triumphed, he would gain the throne; he imagined the disorder, where the heat of battle would arouse pity in the janissaries; he saw them already armed to defend him against Suleiman's barbarity; he believed he could hear himself proclaimed emperor by the whole army. This was indeed exactly what Suleiman had feared, and he had taken the precaution of hanging up curtains behind his tent, where this tragedy took place, so that nobody could see anything or even suspect anything and no noise could be heard. Yet Mustafa's ardent desire to live and reign made him invincible, although alone against them all; the result of the combat was still uncertain, but Suleiman on the other side, impatient for success, raised his head above the hanging and saw that his mutes were ready to succumb; his fears were greatly increased and he looked menacingly at them, his eyes full of anger, and filled with cruelty at their lack of courage. What was the effect of this look on the mutes? I cannot describe it; the fury he exited in them was without parallel. They instantly threw themselves on Mustafa for a second time, knocked him straight down and snatched his life from him; they immediately exposed the body of the unfortunate prince on a carpet in front of Suleiman's tent so that the janissaries should understand his power and authority from the fate which had just been inflicted on the man they wanted to have as emperor".

Ogier Ghiselin de Busbecq, Ambassador to Ferdinand I, from an eyewitness account appearing in his Letters, 1555-1562.

One of the great failings of Imperial Rome was that it never developed a consistent law of succession. When an emperor died, usually by assassination, a violent and bloody struggle for the throne would frequently ensue. The struggle could be so great that it exploded into all out civil war, particularly notable examples being those that followed the death of Nero in 68 AD and of Commodus in 192 A.D. The empire would be torn apart, hopelessly divided until a victor emerged. The enemies of Rome would often try to take full advantage of the chaos, with the inevitable effect of a progressive weakening of the empire. The newly arrived tribes, of the Thirteenth century, the Ottoman Turks, well understood the perils of succession - perhaps by their own innate insight or perhaps because of their increasing contact with Byzantium. They would aim to learn from their western neighbors and circumvent the danger that succession posed to the unity of their own rapidly expanding empire.

In old Turco-Mongol culture the eldest son of the family held a special precedence in many ways, however by law, every member of a family had equal rights when it came to the laws of familial inheritance. Needless to say this posed its own problems on the death of a Sultan. While the succession was firmly rooted in the old House of Osman - which not even a powerful grand Vizier would dare challenge - this is not to say the individual sons of the Sultan were above challenging each other for the throne, even if the recently deceased sultan had nominated a successor. The "solution" that emerged was as pragmatic as it was brutal. It came to be understood that that whichever son became Sultan, he had the right, indeed, it was a practical imperative of his own survival, to have executed the rest of his brothers. This understanding became legitimatized into the Ottoman legal code by Mehmet II in a chilling decree he pronounced as follows:

"Most legalists have declared as permitted that whichever of my illustrious sons or grandsons attains supreme power can sacrifice his brothers to maintain the peace of the world; they should take the appropriate measures".

Mehmet's decree had established a terrible legacy. Suleiman the Magnificent, the greatest of all the Sultans, had his own son Mustafa murdered in front of his eyes, when he deemed that his son was becoming too popular with the army, and would pose a threat after his death, to another of his more favored sons from a another of his wives. Murad III, the grandson of Suleiman the Magnificent, would have five of his brothers murdered within days of becoming Sultan. Mehmet III, his successor would reach the apotheosis of the "Law of Fratricide", by having no less than 19 brothers as well as their 15 pregnant concubines murdered within days of his ascension to the throne. Enough was enough. By the end of the Sixteenth century the Law of Fratricide, would be abandoned for the "kafes" or the "cage". This simply meant that on attaining the throne, instead of having all one's brothers murdered, they were instead imprisoned. Although less barbaric than having siblings murdered, it was only barely better in many cases. Brothers of the sultan were faced with perpetual imprisonment in the fourth court of the Seraglio. Occasionally however when a Sultan unexpectedly died or was forcibly removed, one of these sons, knowing nothing of the world, would be thrust upon the throne. This would needless to say on most occasions produce a weak and ineffective ruler, however quite astonishingly on a few occasions, some proved more than capable of ruling the empire despite their isolated and brutally deprived upbringing.

Although by today's standards the Ottoman Law of Fratricide is considered barbaric and inhuman, it nonetheless, when compared with the free for all, that constituted the succession process of Imperial Rome, was remarkably effective in preserving the internal unity and as a consequence the external strength of the Ottoman state. While the death of a Roman emperor could mean years of bloody and immensely destructive civil war, the death of the Sultan spelt only doom to those unfortunate enough to be members of his immediate family. Today (in Australia) we live in a more refined world were government changes hands not by assignation, civil war, or fratricide, but by a system admittedly not yet perfect, but a vast improvement on bygone ages - the democratic right of us all, to vote!

In past times when we looked to a biomedical marker of myocardial damage, we looked to CK. This however had a great many failings - a poor and non-specific marker - but it was all that we had. In an effort to improve on this the CK-MB fraction was hailed as the "solution" - which, like the Law of Fratricide, was by no means perfect, but was a good deal of an improvement on its predecessor! Today of course we live a more refined world, CK has been replaced by a far better biomarker in the form of troponin I - yet the CK biomarker still has its uses!

CREATINE KINASE - (CK)

Introduction

Creatine kinase (CK), (also known as creatine phosphokinase or CPK) is a ubiquitous enzyme involved in cellular energy storage and utilization.

It is found primarily in heart, brain, and skeletal muscle tissue.

It is used as a biomarker primarily for the detection of skeletal muscle pathology as it is the most sensitive indicator of muscle injury, as well as being the best measure of the course of muscle injury.

It is a non-specific biomarker and can be elevated in many diverse conditions that affect skeletal muscle.

Physiology

Function of CK

CK is primarily located within mitochondria, on myofibrils, and in muscle cytoplasm.

It is involved in **cellular energy storage** and **energy transfer** via two main mechanisms:

- It catalyzes the production of high energy ATP via transfer of a phosphate from creatine phosphate, (which is the major storage reservoir of energy during muscle at rest), to ADP (adenosine diphosphate).

- It participates in the transfer of high energy phosphate from its site of production in the mitochondria into the muscle cell cytoplasm where it is used during muscle contraction.

Muscle enzymes

The enzymes most commonly measured for muscle disorders include:

- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Aldolase

The isoenzymes of CK

CK is a dimer molecule (with M and B subunits) that exists in three distinct isoenzyme forms:

- MM
  - ♥ Skeletal muscle has the highest concentration of CK of any tissue.
  - ♥ Normal skeletal muscle CK has 99 % MM and small amounts of MB (1%)
- MB
  - ♥ Cardiac tissue has the highest concentration of CK-MB. About 20 percent of cardiac CK is CK-MB
  - ♥ In the past CK-MB was the biomarker used for myocardial damage, until it was replaced by troponin I
- BB
  - ♥ Brain tissue CK consists of 90 % CK-BB and about 10 % CK-MM

Macro CK

Macro CK is a term used to refer to CK that is complexed with proteins. Two types of macro CK are recognized:

- Type 1 macro CK: CK complexed with immunoglobulin
- Type 2 macro CK) CK complexed with other undetermined proteins

These macro CK complexes are more slowly cleared from the circulation than normal CK, leading to more persistently elevated levels of CK

Dynamic CK-MM/ CK-MB ratios:

The concentration of MB in skeletal muscle can increase transiently in some acute conditions including:

- Inflammatory myopathy
- Muscular dystrophy
- In the resting muscles of elite athletes, and in many individuals after extreme exercise.

An increased ratio of serum CK-MB measured in inflammatory myopathies or in athletes after extreme exertion may be confused with myocardial infarction, (one reason why CK-MB has be superseded as a cardiac marker by troponin I).

These changes are thought to be due to the increased number of actively *regenerating* muscle fibers in these conditions. Regenerating muscle fibers revert to the primitive fetal state of increased MB production.

Normal Values

A normal total CK level is generally taken as **< 200 U/L**

Interpretation

Causes of an Elevated Creatine kinase

Causes of an elevated CK level include

1. Fever/ sepsis, (of any cause).
2. Rhabdomyolysis, (of any cause)
3. Trauma in general:
    - Elevations can occur with relatively minor trauma such as an intramuscular injection.
4. Snake envenomation
5. Strong physical activity:
    - e.g. Marathon runners
6. Seizures
7. Myocardial infarction
8. Hyperthermia (of any cause):

    Including hyperthermic drug reactions:

    - e.g. serotonin toxicity, malignant hyperpyrexia, neuroleptic malignant syndrome.
9. Electrical injury
10. Intrinsic muscle infection:

- e.g.: Necrotizing infections, gas gangrene/ Clostridial myonecrosis/ necrotizing fasciitis

11. End stage renal disease

12. Drugs:

    Muscle enzymes can be elevated in a number of drug-induced myopathies including those caused by:

    - Colchicine
    - Antimalarials
    - Cholesterol-lowering drugs (**statins**, gemfibrozil, nicotinic acid, and clofibrate)
    - Cocaine
    - Alcohol.

13. Intrinsic inflammatory myopathies including:

    - Muscular dystrophies
    - Periodic paralyses
    - Endocrine myopathies:
        - ♥ Hyperthyroidism/ hypothyroidism
    - Various metabolic myopathies, (these are rare)

14. Inflammatory myositis, of any cause:

    - Polymyositis/ dermatomyositis

15. Stroke or other brain injury, (primarily CK-BB).

Peak levels

In general, **marked** elevations of serum muscle enzymes are seen in myopathies.

A serum CK level of **>1000 units/L** therefore helps to distinguish a primary muscle disease from a neurogenic cause of weakness and muscle atrophy. More modest elevations of CK can occur in some primary neurologic disorders, particularly motor neuron disease.

Time course of CK elevation and decline

In general terms serum muscle enzyme concentrations can be elevated either

- Acutely (as in reversible causes of rhabdomyolysis)

Or

- Chronically (as in most intrinsic myopathies)

In patients with myocardial infarction, the increase in serum CK is short-lived (they rise within 4-6 hours, peak at around 24 hours and fall again within 2-3 days) while that of AST and LDH and troponin I is much more persistent, (up to 10 days). Peak levels of CK do not correlate well with the extent of injury, rather it is the total area under the curve of the levels versus time graph, that correlate more closely with this.

In regard to drug induced myopathies, serum CK concentrations can range from mild elevations of three to four times normal with antimalarial neuromyopathy to 10 - 20 fold elevations in colchicine neuromyopathy and to massive elevations and rhabdomyolysis with cocaine use or acute alcoholic myopathy. Very high elevations of CK may occur in patients on mechanical ventilators paralyzed with non-depolarizing muscle blocking agents.

The degree of CK elevation in dermatomyositis and polymyositis varies greatly. Levels can reach as high as 100 times normal on occasions. Levels may normalize with steroid treatment, but they can also remain elevated in more severe disease.

In cases of rhabdomyolysis the degree of CK elevation correlates with the risk of acute renal failure. Unlike chronic myopathies, however levels decrease rapidly back to normal following resolution of the cause.

After vigorous exercise serum CK concentrations typically peak levels at 8 to 24 hours after exercise and then begin to decrease at 24 to 48 hours, returning to normal levels by about 72 hours. The peak in CK levels corresponds to both the intensity and the duration of exercise. Levels are greater in non-athletes than in athletes.

Indications for Testing

The commonest indications for testing include:

1. Patients with suspected rhabdomyolysis, (of any cause).

2. Patients with suspected myopathies (i.e. intrinsic skeletal muscle pathology) - these may present with myalgias, unexplained weakness, muscle tenderness:

    - Myositis, of any cause

    - Muscular dystrophies

- Periodic paralyses
- Endocrine myopathies

3. Suspected hyperthermic drug reactions.

4. Snake bite

5. Monitoring the course and response to therapy of certain muscular disorders and of cases of rhabdomyolysis.

References

1. Miller M.L et al; "Muscle enzymes in the evaluation of neuromuscular diseases"; in Up to Date Website; November 2012.

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