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An Anesthesia Experience in a Non-traumatic Patient with a High Level of Isolated Creatine Kinase

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Muscle tissue may be damaged as a consequence of both mechanical and metabolic factors. Serum levels of skeletal muscle enzymes or proteins are markers of the functional status of muscle tissue. Creatine kinase, lactate dehydrogenase, aldolase, enolase, aspartate aminotransferase are the most useful serum markers of muscle injury. However none of them are as specific as creatine kinase. Persistent elevation of serum creatine kinase in individuals with normal neurological and laboratory examinations has been called idiopathic hyperCKemia. The management of patients with persistently elevated serum levels of creatine kinase, usually without clinical symptoms, is a difficult and puzzling problem for anesthetists. By the presentation of this hereby the case report herein, it is aimed to share the experience gained from a patient, who has been diagnosed with idiopathic hyperCKemia.

Keywords: Creatine kinase; idiopathic hyperCKemia; anesthesia; TIVA.

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1. INTRODUCTION

Creatine kinase (*CK*), as also known as creatine phosphokinase, is a large intramuscular protein made up of two distinct polypeptide subunits, M and B. Three isoenzymes of CK are found in human tissue: CK-MM (*skeletal muscle*), CK-MB (*cardiac muscle*), and CK-BB (*brain*) [1]. Serum concentrations of CK are increased after muscle is damaged by physical or biochemical injury. This has been reported after strenuous physical activity, trauma, crush injury, myositis, muscular dystrophy, intramuscular injection, convulsions, myocardial infarction, malignant hyperthermia and drugs such as aminophyline and succinylcholine [2-4].

Chronic elevation of serum CK levels is a common manifestation of neuromuscular disorders [1]. Persistent CK elevation is occasionally encountered in subjects without any clinical manifestation of a neuromuscular disorder or any condition known to be associated with increased serum CK levels. The term "idiopathic hyperCKemia" (*IH*) was first coined in 1980 by Rowland et al to describe a condition characterized by unexplained persistent serum CK elevation unaccompanied by neurologic abnormalities [5]. Though clinically asymptomatic, IH patients are potentially susceptible to malignant hyperthermia (*MH*).

In this article, it was is intended to share the experience of general anesthesia of in a case, where the high levels of isolated CK is were present, which is non- proportional with the trauma that the patient had suffered, in the light of the patient data, as well as the literature.

2. CASE PRESENTATİON

It was planned to perform an immediate vein-nerve-tendon repair on a 35-year-old male patient due to a deep laceration in the first and second fingers of the right hand. In this case, in which no previous history of medical operation was present, no anomalies were identified except of the convergent strabismus that was revealed in the physical examination and the heightened CK levels, (*1369U/dl*) that was revealed by the laboratory assessment.

The case was immediately taken into evaluation in terms of due to the high levels of serum CK. It was then surmised that the laceration in the hand would not have such a high enzyme level. From the case history, it was further concluded that there was no excessive muscle activity that might have lead to high CK levels, and there was no endocrinological anamnesis such as thyroid or para-thyroid and there is was also no current use of medicines either (*statins etc.).* No further pathologies were detected during the neurological examinations, except of the convergent strabismus.

In other routine preoperative haematological and bio-chemical lab tests, no anomalies were detected. As a result of the EKG assessment, no findings were detected except of a mild right bundle-branch block. In the meantime, it was found out that the subject had been examined at our hospital on different dates for different problems. When the lab examinations were evaluated, it was found out that both CK values of the patient (*at 3 and 7 months old*) were high as well (*1242U/dl and 1374U/dl respectively*).

In the light of such the accumulated information, it was decided that the patient-case may have been suffering from idiopathic hyperCKemia. However, there was no time for a muscle biopsy and or for an EMG examination, which may have verified such a diagnosis. In case if the diagnosis was right, then we may have been facing a potential risk of a malignant hyperthermia. However, the contracture testing with halothane and caffeine, which is used to determine the susceptibility for malignant hyperthermia, could not be performed either.

The patient was informed regarding the pre-diagnosis (*idiopathic hyperCKemia*) and the risk that this pre-diagnosis may cause malignant hyperthermia (MH). And he was also advised to have the operation by regional block (*continued axillary brachial block*). However, the patient persistently indicated that he would like want the regional block application and further stated that he accepted the risks and preferred the general anesthesia.

It was decided to implement Total Intravenous Anesthesia (TIVA) against the risk of MH. For this purpose, a disposable respiration circuit and an anesthesia device, containing fresh soda lime were utilised. In addition to the standard monitoring procedures, (*heart rate, 5 lead electrocardiography, pulse oximetry, noninvasive blood pressure and end-tidal carbon dioxide=*$ETCO_2$), a detailed additional monitoring that included temperature tracking and neuromuscular conduction, was implemented to the patient that had been taken into operation room. The induction of anesthesia was initiated

with sodium thiopental (4mg.kg^{-1}), and fentanyl (1mcg.kg^{-1}). In the patient, for whom the atracurium besylate (0.6mg.kg^{-1}) was administered to for the purpose of muscle relaxation, the intubation was carried out within 105 seconds according to the data from peripheral nerve stimulator (Train of Four [TOF]).

The management of the anesthesia that followed the intubation was provided with a pre-determined TIVA protocol. We infused propofol at 10 mg. kg^{-1}. h^{-1} for the first 10 min, 8 mg. kg^{-1}.h^{-1} for the next 10 min, and then at 5-6 mg. kg^{-1}. h^{-1} for the duration of the procedure. Remifentanil was maintained at 0.5 mcg. kg^{-1}. min^{-1} throughout the procedure and 2 lt O_2 / 2 lt Air min^{-1}. were applied too. During the operation that lasted 449 minutes (7 hrs and 29 mins), the hemodynamic data and all other corresponding lab data maintained remained at normal boundary levels (Table 1).

At the end of the operation, the patient, whose muscle relaxing effect was antagonized, was extubated when the TOF value was 90%. The patient, whose follow-up values were normal at in the recovery room as well, was then taken into the Intensive Care Unit (ICU) for monitoring. The patient's whose vital stats were normal, except of for his high CK values, and he was sent out to service level 24-hours later. The patient's, whose total CK levels remained to be high on the 1st, 3rd, 5th and 7th post-op days, and was discharged to his home on the day 9th day, in on which day the surgical recovery is was deemed to be completed. However, even in this case, the CK levels were still high (1293U/dl) (Table 2).

3. DISCUSSION

CK plays a key role in the energy transport and storage of the muscle cell [6]. Its highest concentration is in skeletal muscle, cardiac muscle, and the brain. Minimal amounts are present in the intestines and lung, but none is found in the lever [6-7]. CK measurement in serum has remained the best overall marker for detection and monitoring of skeletal muscle diseases and damage [4]. Other enzyme markers for skeletal muscle injury: aldolase, enolase, aspartate aminotransferase, and lactate dehydrogenase isoenzyme 5 are not as specific as CK [4].

An elevated CK level presents a diagnostic dilemma for physicians. Because elevated CK levels are an important marker of myocardial infarction, neuromuscular disease, and rhabdomyolysis [8]. Other conditions that can cause elevated CK levels include pregnancy, malignancies, hyperthermia, thyroid and parathyroid diseases, or even physical exercise [8]. Occasionally, elevated CK levels are observed among people without any symptoms.

The term "idiopathic hyperCKemia" (*IH*) was coined by Rowland et al for cases where there was no clinical or histopathologic evidence of neuromuscular disease [5]. IH is a persistently elevated serum concentration of CK i.e., at least 3 serum CK levels more than twice normal over at least 3 months, without weakness or other significant neuromuscular symptoms [9]. In our case, the elevated CK levels, that were not supported by any pathological findings, from 3 and 7 months ago, were present (*respectively 1242U/dL and 1374U/dL*).

Persistently elevated serum concentration of CK usually accompanies muscle weakness in patients with myopathies. However, it may also be found in individuals with a normal neurological examination, possibly due to subclinical or

Table 1. The change of the CK, blood gas, $ETCO_2$ and core temperature over time during the operation

	1st h	2nd h	3th h	4th h	5th h	6th h	7th h
CK (U/dl)	1422	1458	1521	1579	1601	1638	1639
pH	7.382	7.375	7.391	7.388	7.364	7.377	7.384
PaO_2 (mmHg)	198	196	188	184	191	196	182
PaCO2 (mmHg)	38.2	37.4	36.3	37.7	38.6	37.1	38.8
HCO3 (mmol/L)	3.56	3.73	3.68	3.59	3.77	3.85	3.66
$ETCO_2$ (mmHg)	37	36	35	37	38	36	38
Temparature (^{0}C)	37.3	36.8	36.6	36.4	36.1	36.3	36.4

Table 2. The course of the CK values during the post-op days

	1st day	3th day	5th day	7th day	9th day
CK (U/dl)	1562	1498	1411	1378	1293

preclinical neuromuscular disorders, dystrophinopathy carrier state, hypothyroidism, hypoparathyroidism, alcoholism, or intake of statins and other drugs, and this condition is labeled asymptomatic hyperCKemia [8,10,11]. As the a result of the muscle biopsy of the patient, which was performed during the days that the patient stayed in the hospital after the operation, only "*a slight variation in fiber size*" was identified. Immunocytochemical analysis was normal and also ultrastructural examination did not show any significant lesions. Additionally electromyography (*EMG*) yielded normal results in the case. As the a result, the neither the muscle biopsy nor the EMG, failed to explain the heightened CK levels.

MH is an inherited, pharmacogenetic skeletal muscle disorder involving the dysregulated myoplasmic Ca2+, hypercontracture, and hypermetabolism in response to an exposure to potent volatile anesthetics with/without depolarizing muscle relaxants [12]. The association of IH with MHis as yet unresolved and disaccord anesthetic problems. Anesthesiologists and critical care intensivists as well as primary care physicians should keep this in mind when seeing patients with asymptomatic hyperCKemia and potentially inform them about the possibility of developing MH if exposed to triggering agents.

On the other hand; several predisposing clinical myopathies such as strabismus (*as in our patient*), ptosis, myotonic dystrophy, muscular dystrophy and Marfan'ssyndrome have been associated with MH [13].

Potent inhalation agents and succinylcholine are to be avoided in MH-susceptible patients If possible, local or regional anesthesia is preferred. Anesthesia may be induced with a barbiturate, benzodiazepine, or hypnotic agent and the patient ventilated with 100% oxygen. Fentanyl or other opioid may be added to ensure adequate depth of anesthesia. The trachea is intubated with use of a short-acting or intermediate-acting nondepolarizing muscle relaxant. Anesthetic maintenance is achieved using oxygen and nitrous oxide, an opioid, and a nondepolarizing relaxant as required. TIVA is a good choice for anesthesia as well. Vital signs are monitored with very close attention to capnography [14].

Therefore, the possibilities in this case, which might trigger the MH were intended to be prevented as much as possible. For this purpose, a breating circuit, in which it's the inhalation area inside of it was removed by the flow of fresh oxygen and an anesthetics machine with fresh soda lime present, which was never introduced to any inhalation agent, were prepared. Atracurium besylate, which is a non-depolarizing agent, was used for the muscle relaxation during the induction of the anesthetics. The anesthetics management was provided by administering intravenous anesthetics and an opioid agent by an intravenous infusion pump within a certain/standard dosage protocol that would ensure a sufficient depth of anesthesia, therefore in the form of Total Intravenous Anesthesia (TIVA).

The induction of anesthesia was carried out by thiopental sodium. This agent, which has been in use for the practice of anesthetics for a long time, is a intravenous anesthetic drug, whose profile of effectiveness and adverse effects are well known. In addition, there are only a few publications, pointing out the development of MH during its use [15]. However, it is also acknowledged that long term application of intravenous infusion may lead to the delays on the patients to come out of anesthesia due to the accumulation of the drug in adipose tissue. Propofol on the other hand, is a intravenous anesthetic drug that does not lead to the accumulation on the adipose tissue even after the long term application of intravenous infusion and which provides faster and clearer waking up effect due to faster elimination half-life, compared to thiopental sodium It is also a drug, on which there are positive [16,17] and negative publications [17-19] that contradict with each other regarding its use on MH patients. However, just like thiopental sodium, it is in the category of agents that do not trigger MH as well. Regarding the use of those two drugs, which are listed amongst the safe to use drugs for in MH, we opted to use thiopental sodium, in order to induce fast, deep and safe anesthesia, in combination with propofol, which has an ideal/perfect profile in terms of TIVA. And we believe that our choice provided grounds for a smooth operational procedure during the anesthesia management of the case. However we know both of thiopenthal sodium and propofol dont trigger MH [20].

A clinical MH crisis is characterized by hypermetabolism with variable signs and symptoms, including generalized or localized muscle rigidity, hypercarbia, fever, acidosis,

myoglobinuria, tachycardia, increased serum levels of CK, hyperkalemia, arrhythmias, and, potentially, cardiac arrest and death if untreated [9]. Therefore the vital stats, which included the temperature and $ETCO_2$ values, which were essential to detect the very first signs and symptoms of a MH crisis that may occur in the case, in an early manner, were carefully observed from the monitors. In addition, the hourly blood gas and CK stats, as well as the micturation of the patient, was observed too. (Table 1). The sole change of CK later in the operation, without observing any changes in other lab stats, was not considered as pathological; Because it is well-known that the a surgical procedure also induces a trauma on the patient and the position of the patient, prolonged surgical operation and even the intracranial neurosurgery are also known to elevate the CK levels [21-24].

MH episodes are very rare and modern anesthetic techniques, such as increasing use of non-triggering intravenous anesthetics and avoidance of succinylcholine are likely to make it even rarer, leading to the potential risk of reduced awareness of anesthesiologists for MH. When MH was first recognized as a complication of anesthesia, the mortality rate was 70-80%. Nowadays, the mortality rate is estimated to be less than 5%, with early detection of MH episode, using capnography, prompt use of the drug dantrolene, and the introduction of diagnostic testing [25]. Even though the mortality rates of MH are low, according to a recent study by Larach et al., the morbidity rate of MH is 34.8% [26].

The "gold standard" for diagnosis of MH is currently the *in vitro* caffeine halothane contracture test (CHCT). In vitro CHCT was performed according to the caffeine-halothane contracture protocol of the European Malignant Hyperpyrexia Group on fresh specimens of vastus lateralis muscle [27]. Briefly, patients were considered MH susceptible (MHS) if a contracture of at least 2 mN occurred after exposure to 2 mM caffeine and 2% halothane, MH equivocal if muscle specimens contracted in response to only one of the triggering agents, and MH negative if contracture response was normal to both drugs. The clinical implications would be underscoring the importance of this as a susceptibility to developing MH.

In one study, malignant hyperthermia susceptibility was discovered in 49% of IH patients [9]. Lingaraju and Rosenberg report positive CHCT results in three of seven individuals with persistently elevated CK levels [28]. Another series of 37 patients with persistent elevated CK levels disclosed one patient malignant hyperthermia susceptibility (*MHS*) by CHCT and one patient MH equivocal by CHCT [29]. In a recent review of individuals with IH, the authors found a high percentage of autosomal dominant cases and no specific findings [11]. In most cases, pathogenesis is unknown and clinical management is unclear. Though clinically asymptomatic IH patients could be susceptible to MH. Therefore, Weglinski and colleagues advised that all patients with IH who have muscle biopsy should also receive malignant hyperthermia contracture testing [9]. Within this context, in the CHCT test, performed on the patient one month after the operation, MH susceptibility only for halotan was detected.

Management of patients with elevated serum CK in the absence of a diagnosed clinical syndrome or enzyme defect is problematic. In some patients, the CK elevation may fluctuate, and in others, it may be a normal variant. Episodes of MH and MH-like events in patients with isolated elevation in CK have not been reported. Otherwise, there is no evidence that brief, i.e., <15 min, exposure to modern inhalation anesthetics is harmful in these patients or in patients with enzyme defects, nor is proof available that propofol is safe. Accordingly, the evidence for an association between asymptomatic hyperCKemia and MHS is weak, but it is also not impossible either.

4. CONCLUSION

In the practice of anesthesia, we sometimes encounter with patients with elevated CK levels. Despite advanced diagnostic procedures in muscle disorders, CK activity is still one of the parameters mostoften investigated in serum. Occasionally,marked elevated CK activity requires detailed diagnosticwork-up, including electrophysiological, histopathologicaland genetic studies. However, it is not always possible to examine or analyse the cause of the elevated CK levels due to the urgency of the operation, (*especially in terms of EMG examination and muscle biopsy*) or sometimes due to the inadequacy of the lab facilities of the medical institution (*for in-vitro CHCT and molecular genetic testing*).

There is still a group ofpatients with so-called idiopathic hyperCKemia and withno evidence of

neuromuscular disorder. As little is known about potentially asymptomatic hyperCKemia, these patients should be carefully monitored. In addition, it should be remembered that the elevated CK levels pose a non-negligible risk in terms of malignant hypothermia.

A 'clean' anaesthetic machine is used by using a new breathing system. Contact with volatile agents and succinylcholine is absolutely contraindicated. Regional anaesthesia should be used if possible. If general anaesthesia is unavoidable, (*in terms of the operational region or as demonstrated in this case report, when the regional anesthetics proposal is rejected by the patient*) then TIVA with propofol is recommended. Monitoring of end-tidal carbon dioxide concentration, ECG, arterial pressure, oxygen saturation and core temperature is mandatory.

In addition, today, where the pre-operative tests are increasingly being limited to to cost effectiveness and ever-increasing medical expenses, in cases, where suspicions arises and especially in the cases, where the congenital benign musculoskeletal deformities are present, we also think that serum CK measurement should not be ruled out either.

CONSENT

Written informed consent was obtained from the patients for the publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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