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EC CARDIOLOGY
Case Report

Oxidative Stress and Anaphylaxis in Polytherapy: Discussion of a Clinical Case

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Received: January 19, 2019; **Published:** January 29, 2019

Abstract

Oxidative stress is the body's inability to clear out free radicals such as reactive oxygen species and reactive nitrogen species that can cause harmful effects, and there are several biomarkers used to detect these species only they need specialized laboratories for them to be precise. Cytochrome P450 are special enzymes that acts on neutralizing oxidative stress throughout the body by carrying out oxidoreduction reactions, as well carrying out the metabolism of most medications taken by patients. In this unique case, results shows that multi-drug therapy played no role in the induction of oxidative stress nor anaphylaxis, rather it was clearly a case of genetic mutation complicated by molecular dysfunction inside the patient's cells. These mutations affected the cytochrome's metabolism ability leading to a full-blown anaphylaxis accompanied by skin necrosis, muscle death and multi-organ failure.

Keywords: *Oxidative Stress; Cytochrome P450; Anaphylaxis; Multi-Drug Therapy; Genetic Mutation; Molecular Dysfunction*

Introduction

Oxidative stress is defined as the body's inability to detoxify free radicals and their harmful effects through neutralization by antioxidants. Free radicals are oxygen-containing molecules with one or more unpaired electrons, thus making it a highly reactive and toxic compound to the human body; these free radicals can be classified into two species: Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). RONS are produced by all aerobic cells and have an important role in aging and its related diseases. Though some of these reactive by-products are toxic, some of them are quite beneficial due to their anti-pathogenic effects. The interaction of these free radicals with cell components (DNA, Proteins, Lipids), causes them to lose their electrons thus become unstable leading to several pathophysiological conditions (Parkinson, Alzheimer, Cancer, Type II Diabetes and anaphylaxis) [1,2].

Nowadays, there are several biomarkers tested to identify oxidative stress inside the body, only they are not very cost-effective; as well requires specialized laboratories and equipment to ensure correct and definite results since they can be easily affected by external factors (Air, molds and bacteria). These biomarkers are used to identify a wide variety of diseases (cancer, diabetes mellitus, neurodegenerative diseases and environmental sensitivities) and most important biomarkers tested are glutathione peroxidase, superoxide dismutase (SOD), lipid peroxide and total antioxidant capacity [3].

Cytochrome P450 are hemoproteins, which uses a broad variety of substrates for most of the enzymatic reactions inside the body, in other word, they are the last oxidase enzymes in the electron transport chain system [4]. These membrane-associated proteins, which are found either in the inner mitochondrial membrane or in the cell's endoplasmic reticulum, metabolizes a wide variety of drugs, several hormones (estrogen, testosterone), synthesize cholesterol and metabolizes vitamin D.

Various drugs can alter the concentration of CYP's in the body through either induction or inhibition and since CYPs enzymatic activity can affect the breakdown of several drugs; this can be considered as a major drug adverse effect source [5]. In this case meta-analysis, by theory, we will try to link how different cardiac drugs (Clopidogrel, Statins, Angiotensin 1 Blockers and PPI) if taken along OTC drugs (paracetamol, ibuprofen, aspirin, etc.) can affect the cytochrome system (overload production of cytochrome or inhibition) and lead to oxidative stress-induced anaphylaxis. As well, we will discuss all the possible genetic and environmental factors that might contribute in causing this anaphylaxis, so that in the end we can answer two important questions: 1) is oxidative stress-induced anaphylaxis monofactorial? And 2) did the acute oxidative stress occurred from genetic variation (sudden mutation, specific gene activation, molecular alteration, DNA damage) or from an allergic reaction to the drug combination taken by the patient.

Case Description

A 54 YO woman arrived to the ER service in a state of shock, low BP, orthopnea, tachycardia, cyanosis and a skin rash. Her medical history is that of HTN (hypertension), T2DM (type-II diabetes mellitus) and CAD (coronary artery disease). She underwent coronary an-

giography 5 months ago, confirmed double disease, with a critical LAD lesions, she underwent PCI with stent placement and discharged on Clopidogrel, Aspirin, Atorvastatin, Molsidomine, Valsartan and Amaryl. Since that time no problem was observed, later on that day, she felt mildly dyspneic with chest oppressive like sensation, diffused pruritus and itching. Her condition started to worsen with the hours until she decided to visit the nearest ER service.

At arrival blood sample for lab analysis was drawn and she was started on mimetic for her shock condition and supposing a possible allergic reaction; she was given 1 GR solucortef and 1 amp anti-histamine ex-aduvantibus.

Cardiac echo Doppler was performed to evaluate cardiac output resulted in good EF, though hydration therapy was performed with hope to elevate her BP.

Pulmonary x-ray showed unharmed lungs and normal heart size; Abdomen echo showed normal liver, kidneys, gallbladder, pancreas, bile ducts and spleen.

Lab results were those of acute multi-organ failure with elevation of hepatic, pancreatic and cardiac enzymes, in addition to elevated creatinine, BUN, bilirubin, etc.

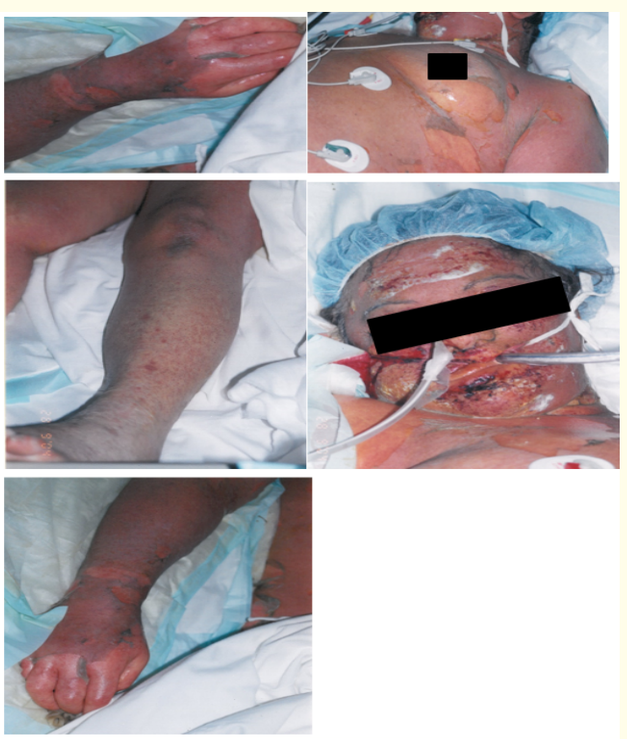
The respiratory condition was also worsening with sever desaturation, though mechanical assisted ventilation was applied.

Her conditions got even worse with refractory response to all treatments, in few hours epidermolysis started to appear and diffuse. Biopsy and cell culture were taken and was started on broad-spectrum anti-biotic awaiting results. Meanwhile, ICU (intensive care unit) program was applied including supportive treatment and Lab FU (laboratory follow up).

The general condition of the patient got worse and worse by the hour with even worse lab results indicating acute refractory multi-system shut down. The more striking event in addition to the multi-organ failure was a concomitant lysis of the subdermal tissues that developed into a more dramatic lytic process involving the muscular system and died within 48h. At the time, a suggestive diagnosis of Lyell syndrome or Stevens-Johnson syndrome and Clopidogrel was accused of being the trigger agent of this dramatic evolution.

This case raised so many important questions about both the evolution and the diagnosis:

1. Why she didn't develop such a reaction before.
2. Does she have a dormant genetic background and in a certain moment, an environmental factor caused an irreversible dramatic lytic process.
3. Was she taking OTC drugs and did these drugs interfered in enzymatic inhibition or induction.
4. Given the high peroxidase levels in her body, was oxidative stress the trigger of the process.



Figure

Blood tests

Hematology			
	Count	**Unit**	**Normal range**
WBC	19200	cu.mm	4000 - 11000
RBC	3.61	cu.mm	M 4.5 - 6.5, F 3.8 - 5.8
Hemoglobin (Hb)	10.2	g/dl	
Hematocrit (Ht)	33.2	%	
Neutrophils	32	%	40 - 60
Lymphocyte	43	%	17 - 39
Monocyte	19	%	2.0 - 8.0
Eosinophils	3	%	1.0 - 5.0
Basophils	3	%	0 - 1
Platelets	371000	cu.mm	150000 - 400000
MCV	92	fl	
E.S.R.	36	mm/hr	
D. Dimer	7.2		< 0.3
Reticulocyte	1.6	%	
Chemistry			
Glucose (FBS)	763.28	Mg/dl	70 - 110
Urea (BUN)	131	Mg/dl	8.0 - 25.0
Uric acid	7.1	Mg/dl	3 - 7.5
Creatinine	3.18	mg/dl	0.7 - 1.3
S.G.O.T.	880.7	IU/L	< 38
S.G.P.T.	368.2	IU/L	0 - 40
Gamma.GT	839.7	IU/L	F 5 - 36 M 8 - 61
Na^+	120	meq/l	135 - 145
K^+	4.7	meq/l	3.5 - 5.1
Cl^-	90	meq/l	98 - 107
CO_2	7	mmol/l	24 - 30
Amylase	233	IU/L	28 - 100
CPK	2361	U/L	< 170
Total Bilirubin	11.22	mg/dl	0.1 - 1.2
Alk. Phosphatase	1594	IU/L	35 - 129
Ammonia	4.3		0.11 - 0.60
Serology			
HBS	Negative		
HCV	Negative		
Haptoglobin	0.01	mg/dl	30 - 200
Direct combs	Negative		
Urine analysis			
WBC	Abundant		
RBC	Numerous		

Table

Arterial Blood gases: All normal.

Spontaneous Prothrombin: 41% (N.V: 20 - 40).

Hemoculture: Hemoculture was positive for *E. coli.*

These lab results are of the blood sample taken after she experienced the allergic reaction; following that another sample was taken later on and resulted in data beyond the machine's reading capability specially the anti-peroxidase.

Discussion

In this part, we will discuss the possible reasons to what caused a massive oxidative stress inside the patient body which in turn lead to a full-blown anaphylaxis; or that might have caused the patient to develop an allergic reaction to certain medications. As well, we will address the role of cytochrome P450 in altering the patient's body chemistry or causing any sudden genetic changes.

Gene mutations inducing oxidative stress

NFE2L2 (Nuclear factor, erythroid 2 like 2) gene is a human transcription factor encoding for the NRF2 basic leucine zipper protein which expresses antioxidant proteins that helps protect against oxidative stress. Huppke., *et al.* ran a case study on several patients who all suffered from the same medical symptoms and concluded that a spontaneous De Novo mutation in the NFE2L2 gene lead to an increase in oxidative stress levels inside the patients bodies and caused these patients to develop a multisystem failure [6]. On the other hand, Akiyama., *et al.* studied the effect of both p62 and NRF2 deletion and concluded that these deletions lead to the development of non-alcoholic steatohepatitis inside the body. NASH caused a massive hepatomegaly, fat accumulation and hyperphagia induced obesity coupled with high resistance to insulin. In addition, the results showed dysbiosis associated with a high level of lipopolysaccharide levels in the feces as well the appearance of a high level of gram-negative bacteria in the gut which caused high amount of gut stress (imbalance of healthy bacteria) [7].

MTHFR (Methylenetetrahydrofolate reductase) gene encodes for the enzyme methylenetetrahydrofolate reductase, which is the limiting enzyme in the methyl cycle. This enzyme is responsible for the reduction process of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, which is a co-substrate for the re-methylation of homocysteine into methionine. Though MTHFR gene variation is a normal process in healthy, other variants can contribute to several complex diseases such as Alzheimer's disease, colorectal cancer and Leukemia [8]. MTHFR has two gene variants leading to severe medical conditions; yet on the molecular level in the case of absence of homocysteine re-methylation, which causes: endoplasmic reticulum stress, glutamatergic receptor activation leading to an influx of Ca2+ levels in the body and damage the DNA affecting the cytochrome P53 system leading to an increase in oxidative stress levels.

HMOX1 (Heme oxygenase 1) gene encodes for the heme oxygenase 1 enzyme which is responsible for the cleavage of heme molecules into biliverdin, carbon monoxide and ferrous iron thus giving this enzyme an anti-inflammatory role by the process of regulating Interleukin 10 and Interleukin 1 receptor antagonist [9]. Poss., *et al.* studied the level of oxidative stress on HMOX1 deficient mice, results showed a histopathological anomalies in the liver tissue, an increase in serum liver enzymes levels, hepatocellular vacuoles and hepatocellular necrotic foci thus concluding that HMOX1 is an essential enzyme for the resistance of oxidative stress inside the body [10].

SOD1 (Superoxide dismutase 1), CAT (Catalase), GPx (Glutathione peroxidase) and GST (Glutathione-S-transferase) gene families encodes in human for their specific enzymes which are crucial for the breakdown of the oxidative stress end-products. All of which can be tested for their levels in order to ensure that the body is capable of avoiding the buildup of reactive oxygen species and these genes are labeled as oxidative stress markers. Therefore, the slightest mutation whether it was spontaneous or site specific can lead to a massive multi-organ failure, cancer, metabolic diseases, autoimmune diseases and other complex diseases. Salminen., *et al.* studied the allelic variations of these genes and their effect on the human brain; concluding that all the variations leads to a buildup of reactive oxygen species thus inducing oxidative stress in the body; resulting in severe brain damage, impaired brain integrity and loss of cognitive function [11].

TXN1 and TXN2 (Thioredoxin 1 and 2) genes encodes for the thioredoxin protein which is responsible for many biological process, most importantly for the redox reactions that breaks down reactive oxygen species [12]. Missense mutation leading to a loss of function of these two genes can have a devastating effect on the developing embryo specifically at 4-cell stage; more importantly leads to a build-up of free radicals in adults that increases the levels of oxidative stress in the body. As mentioned before, Trx regulates several redox reactions in the body of which worth mentioning is donating an electron to peroxiredoxin; encoded by the PRDX gene is a group of ubiquitous antioxidant enzymes which regulates the mediation of signal transduction in human cells; carrying out the breakdown of hydrogen peroxide (H_2O_2) into water molecules [13]:

$$\text{Prx (reduced)} + H_2O_2 \rightarrow \text{Prx (oxidized)} + 2H_2O$$

$$\text{Prx (oxidized)} + \text{Trx (reduced)} \rightarrow \text{Prx (reduced)} + \text{Trx (oxidized)}$$

Therefore, in the case of a mutation in the TXN gene, Trx will not be able to donate the electron in order for the Prx to function correctly. As well, a mutation in the PRDX gene can as well lead to a loss of function of the Prx protein and increases the levels of H_2O_2 inside the body thus increasing oxidative stress.

Molecular dysfunctions causing organ failure

Mitochondrial diseases are diseases caused by mitochondrial dysfunction or a failure in the mitochondrial process; mitochondria are cellular organelles responsible for the creation of more than 90% of the body's energy in order to sustain body organ's function. In the case of a mitochondrial failure, less energy is produced and the cell begins to fall apart even it leads to cell death and if this process continues inside a specific organ it can cause it to fail. Many body organs requires a large amount of energy to function (heart, liver, lungs and brains), therefore in the case of a continuous dysfunction, it leads to a multi-organ failure.

Mitochondrial dysfunction have several symptoms such as seizures, strokes, motor functions disabilities, developmental delays, and digestive problems in addition to several other complex diseases that can range from oxidative stress (and vice versa) to autoimmune diseases even a full blown anaphylaxis.

Mitochondrial dysfunctions results from either spontaneous or inherited mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) which causes a protein or mRNA alterations residing inside the mitochondria thus causing the energy loss inside the tissue-specific cell and leads to its failure [14].

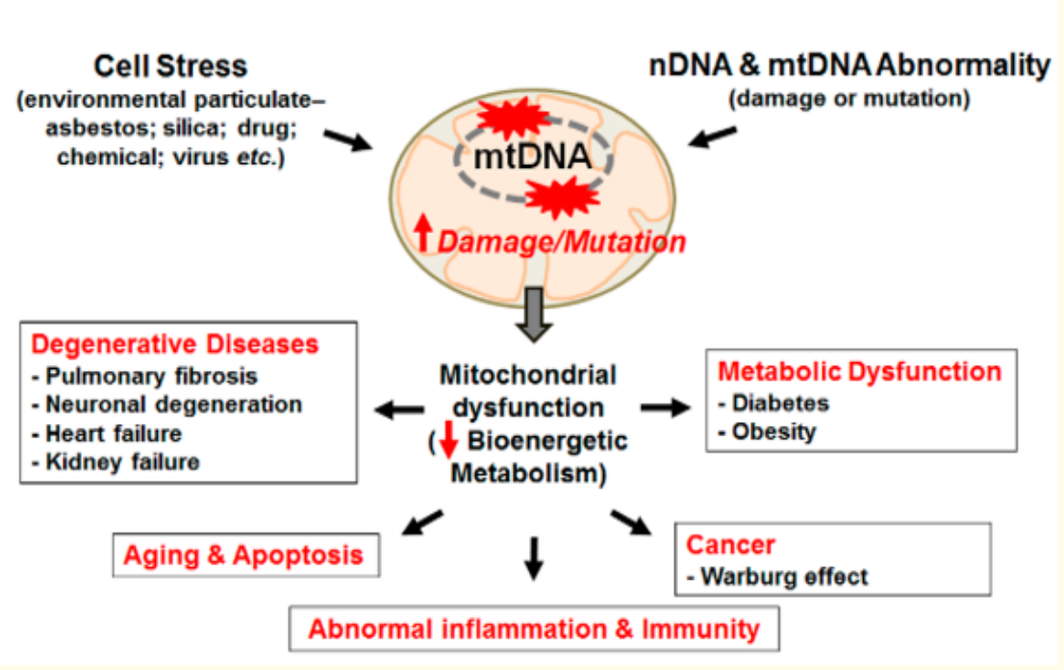


Figure 1: *The effects of cell stress and DNA abnormalities leading to mitochondrial dysfunction inside the patient's mitochondria.*

Cillero-Pastor., *et al.* studied the mitochondrial dysfunction pathway and concluded that this dysfunction causes an activation of cyclooxygenase 2 and prostaglandin E2 inside the human chondrocyte thus provoking an increase in inflammation as well an elevation in oxidative stress levels inside the body [15].

Naturally occurring DNA damage and repair system failure DNA damage is a chemical alteration of the DNA structure that works on changing the structure of the genetic material inside the DNA molecule and causes a dysfunction in the replication and transcription process. This process occurs naturally inside the body through either 1) metabolic process by releasing reactive oxygen species and peroxiding lipids, which are the main cause of oxidative stress in the body. Or 2) hydrolytic process that acts on cutting the chemical bonds between nucleotides [16] which by theory can cause a cascade of molecular alterations that can lead to an acute anaphylactic shock/allergic reaction.

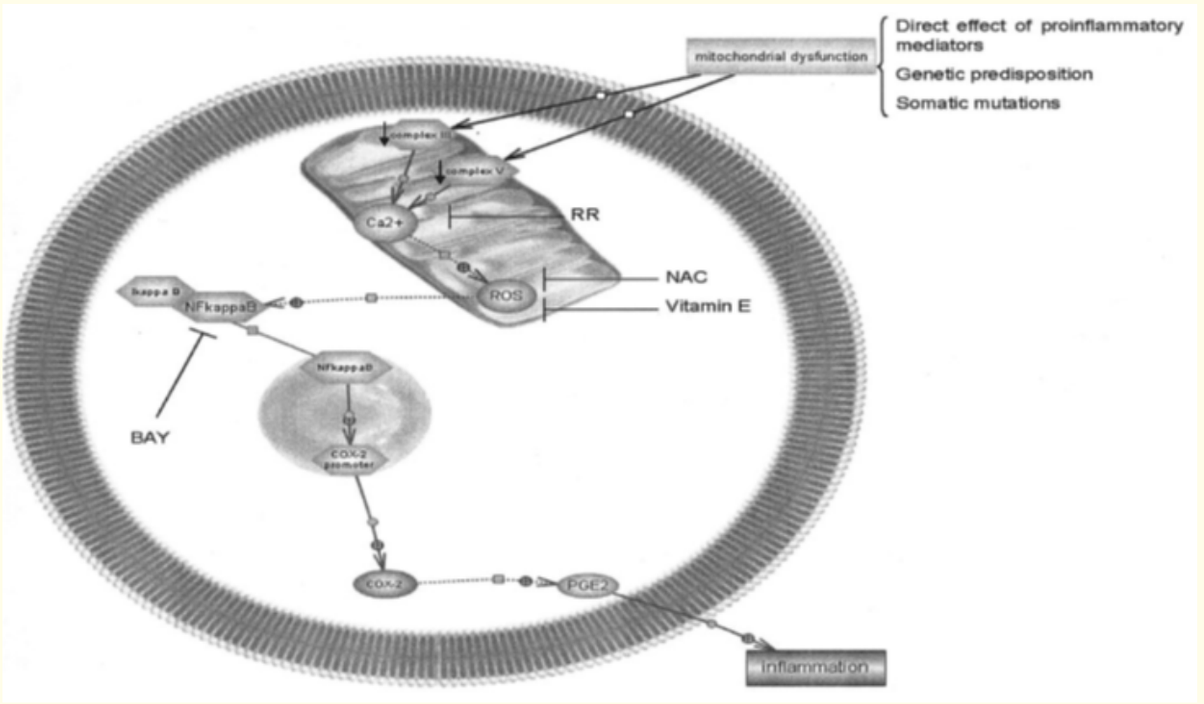


Figure 2: *Schematic representation of cyclooxygenase 2 and prostaglandin E2 activation by mitochondrial dysfunction inside the human chondrocyte.*

There are several factors causing DNA damage, ranging from environmental factors (UV light, Ionizing radiations and mutagenic chemicals) to endogenous factors (depyrimidination, O6-methylguanine and double strand breaks).

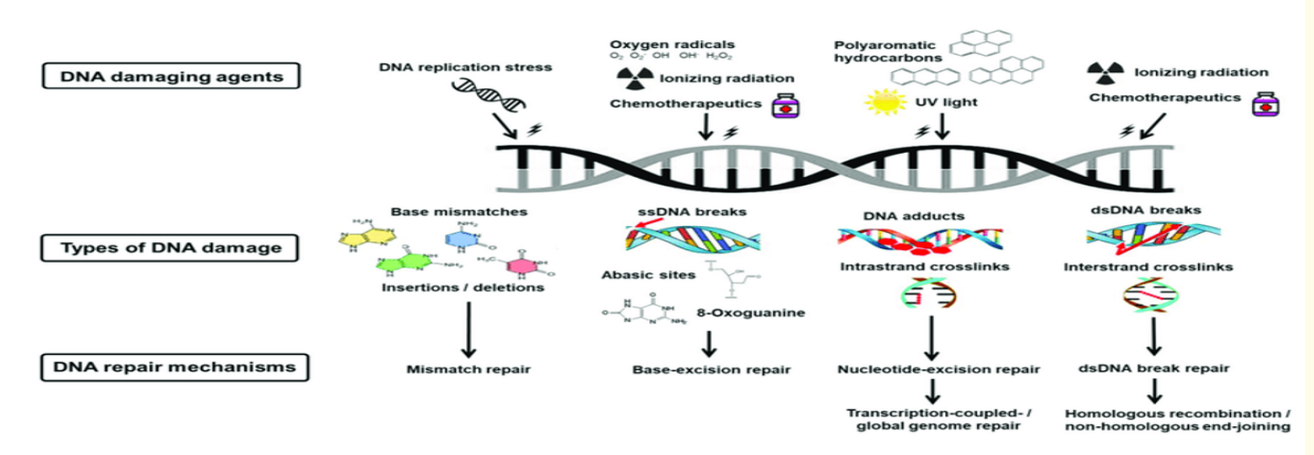


Figure 3: *Schematic representation of different DNA damaging agents, the types of DNA damage and the DNA repair mechanism specific for each damage.*

DNA repair system acts on repairing damage occurred in the DNA strand whether it was single stranded or double stranded, in this category, there are seven different types of DNA damage repair systems, yet for our case, we would mention only five systems.

Base excision repair system acts on repairing damage resulting from oxidation damages (ex. MUTYH pathway), post-translational modifications (deamination, alkylation) as well single strand breaks [17].

Nucleotide excision repair (NER) system acts on repairing damages resulting from oxidative endogenous lesions and thymine dimers formation originating from sunlight radiation [18].

Homologous recombinational repair system acts on repairing damage in the DNA at the S2 and G2 phase pre-mitosis in the cell cycle [19].

DNA mismatch repair system acts on repairing insertion/deletion and substitution mutations (yet not clear in the case of a silent mutation) [20].

Direct reversal system acts on repairing the DNA by reversing 6-O-methylguanine into guanine by means of O-6-methylguanine DNA-methyl transferase (MGMT) [21].

Therefore, any alteration or dysfunction of these repair systems leads to a transcription/replication error, which in turn results in several mutations throughout the cell. Thus resulting in an overload of reactive oxygen species, free radical build up, poisonous chemicals, pre-mature cell death, multi-organ failure, multi-complex diseases, immunity failure, sudden and acute anaphylaxis and cancer formation and metastasis.

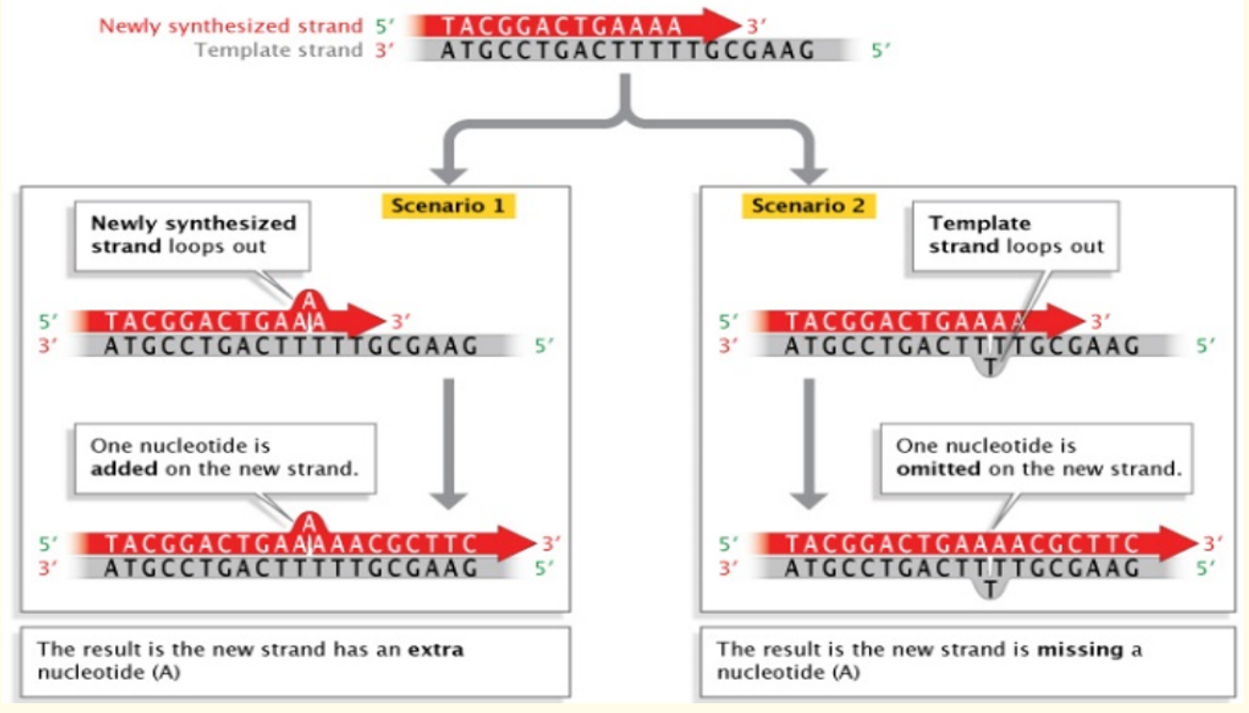


Figure 4: *Schematic representation of the different types of transcriptional errors inside the human cell.*

Vermulst., *et al.* studied the transcription error pathway and its effect on the cell and concluded that, cells that undergoes transcription errors shows an increase in number of molecular chaperons in the cytoplasm, as well they exhibit a proteotoxic stress which decreases the cell's lifespan thus rendering them more prone to cell death. Finally, these errors sensitized cell to genes causing protein-folding diseases [22].

Multi-drug therapy can increase oxidative stress and may inhibit cytochrome activity

In this part, we will discuss the mechanism of action of each drug taken by the patient, what are their side effects and discuss their specific pathways, in order to understand if multi-drug therapy had any role in altering the patient cellular molecular integrity and could have caused a change in the immune system to develop a full-blown anaphylactic shock.

Valsartan is an angiotensin II type 1 inhibitor that is used for the treatment of hypertension, congestive heart failure and increase the survivability in the case of a heart attack. Its main mechanism of action acts by blocking the aldosterone-secreting and vasoconstricting effects of angiotensin II by blocking its binding to its proper receptor (AT1) in several tissues (vascular smooth muscles and adrenal glands) in order to reduce hypertension. It is largely excreted in an unchanged form in man and it is metabolized at a minimal rate as well. Nakashima., et al. (2005) studied the effect of Valsartan on cytochrome activity and resulted that it is metabolized by microsome found in the liver and among the cytochromes that are able to catalyze the active compound (4-hydroxyvaleryl) only CYP2C9 was aberrant among other cytochromes. In addition to the cytochrome, diclofenac was found to inhibit the formation of 4-OH valeryl but had no effect on the cytochrome mentioned before [24]. Side effects includes dizziness, diarrhea, hypotension, rheumatoid arthritis and URI (upper respiratory infections).

Glibenclamide is a sulfonylureas class medication that is used for the treatment of type II diabetes mellitus. It is metabolized through cytochrome CYP2C19 and CYP3A4 and no evidence that this drug has any negative effects on the cytochrome system. This medication acts by binding to ATP-sensitive potassium channels and inhibiting them in pancreatic β-cells, this inhibition causes cellular depolarization which cause the voltage-dependent calcium gated channels to open resulting in a calcium level increase inside the cells thus stimulating insulin production/release. The main side effect of this drug is a medicine induced hypoglycemia and formation of cholestatic jaundice.

Atorvastatin is a statin that acts on lowering lipids and prevent cardiovascular diseases. It acts on inhibiting HMG-CoA reductase (found in the liver, responsible for the production of cholesterol) which reduces HMG-CoA into mevalonate. Reported side effects of this drug includes formation of type II diabetes mellitus, Myopathy accompanied by elevation in creatine kinase (CK and CPK), persistent liver enzymes abnormalities, joint pain, loose stool and muscle pain. Atorvastatin is mainly metabolized by cytochrome CYP3A4 and CYP3A5 and shows no negative effects on the cytochrome system, though it is found to be an inducer of cytochrome CYP3A4.

Cinnarizine is an anti-histamine and a calcium-channel blocker, mostly prescribed for the treatment of vertigo and cerebral apoplexy. Most common side effects of this drug includes lethargy, hypersensitivity reaction, muscle rigidity, chronic Parkinson, presynaptic dopamine and serotonin reduction, somnolence, hypotonia and convulsions. Cinnarizine is metabolized by cytochrome CYP2D6 and shows no negative effect on the cytochrome system.

Aspirin is a salicylate used for the treatment of inflammation, pain and fever. It acts on inhibiting prostaglandins and thromboxane (which prevents the formation of platelets aggregates in blood vessels) by means of inhibiting cyclooxygenase (COX-1 and COX-2). Aspirin side effects varies depending on the patient's condition, characterized by gastrointestinal bleeding (perforating ulcers in the stomach), hemolytic anemia (patients with the genetic disease glucose-6-phosphate dehydrogenase deficiency), tinnitus (ringing in the ears), Reye's syndrome (acute encephalopathy and fatty liver disease), swelling of skin tissues and angioedema. Aspirin is metabolized mainly by cytochrome CYP2C9 and CYP2D6 and shows no negative effect on the cytochrome system.

Molsidomine is a vasodilator that is metabolized in the liver into linsidomine that upon decay releases nitric oxide inside the body causing the blood vessels to dilate and increases the blood flow. Side effects include an abnormal creatine levels, angina pectoris, increase in blood TSH levels (thyroid stimulating hormones) and anemia. The metabolism of molsidomine occurs naturally inside the body without the interference of any cytochrome and this drug shows no negative effect on the cytochrome system. In addition, it is worth mentioning that NO acts as a vasodilator and multi-organ protector, in relation to our case there was a depletion of nitric oxide inside her body that caused a chain reaction of organ deterioration. It is necessary to address to what was the cause of this depletion inside the patient's body and what approach should be taken in order to avoid such problem in future cases.

Clopidogrel is an anti-platelet medication used for the reduction of heart diseases and strokes risk. Two steps activation through different cytochromes, first step through cytochrome P2C19, P2A1 and P2B6 and the second step by cytochrome P2C19, P2C9 and P3A, activate Clopidogrel. After activation, the metabolite irreversibly inhibits the P2Y12 subtype of ADP receptor (receptor activating platelets formation). Interaction with NSAIDs have showed increase in gastrointestinal bleeding. Side effects of Clopidogrel include thrombotic thrombocytopenic purpura, hemorrhage, and rare cases of serious hypersensitivity.

Paracetamol is a non-steroidal anti-inflammatory drug prescribed for the treatment of pain and fever. Its mechanism of action varies from that of aspirin and other NSAIDs by selectively inhibiting cyclooxygenase activity in the brain that makes it a bad example of an anti-inflammatory medication; as well, it shows the modulation of endogenous cannabinoid system in the brain by the mean of paracetamol

metabolites. Side effects include fatal liver damage, fatal skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), asthma and a slight increase in risk of kidney cancer. Paracetamol is metabolized mainly by cytochrome CYP2C9 and shows no negative effect on the cytochrome system.

Lifestyle changes can alter the body's chemistry and help induce oxidative stress

Several lifestyle factors nowadays acts on overloading the body with toxins and induce oxidative stress by constricting blood vessels and increasing acidosis levels (respiratory and metabolic), factors such as stress, anger, sleep deprivation, food diet low in anti-oxidants, chronic fatigue and insomnia and pushing the body's ability beyond its limits. All these factors can help in increasing reactive oxygen species in the body and alters the body's chemistry by promoting genetic mutations, altering cellular molecular integrity and overloading cells to the point of permanent cellular damage.

Cytochrome P450 may have played a role in altering the patient's genetic profile by increasing the oxidative stress level

As mentioned before, cytochrome P450 are important for the breakdown of several drugs, electron transport and redox reactions. Zanger., *et al.* discussed how cytochrome P450 superfamily affect individuals based on their metabolizing capability (poor, intermediate, extensive and ultra-rapid), drug types, and cytochrome types and how these cytochromes are affected inside the body by genetic modifications and epigenetic variations. In the case of our patient, none of the mentioned drugs caused an overload or inhibition of cytochrome activity leading to toxicity, due to the fact that each medication is metabolized by a different cytochrome than another, as well none of these drugs exhibited a drug-drug interaction between them. As for genetic alteration/mutation, Zanger., et al. showed that several people exhibiting genetic modifications and variations could cause cytochrome to lose their ability to metabolize drugs in a correct manner. They discussed that specific SNP's, spontaneous and/or inherited mutations can cause: 1) a cytochrome failure leading to an increase of drug plasma levels as well rendering the patient as a poor metabolizer and leading to acute toxicity and overdose. 2) A cytochrome overload that metabolizes the drug in a much faster way, thus leaving the patient prone to deadly diseases [23]. Therefore, it is safe to say that the genetic variations mentioned above can be a huge possibility that caused cytochrome activity to decrease or get inhibited. As well, mitochondrial dysfunction was found to increase oxidative stress that in turn causes the cytochrome system to crash and rendering it unable to metabolize drugs nor carry out the proper redox reactions to eliminate the build-up of free radicals.

Conclusion

In conclusion, facts prove the idea that genetic variation combined with molecular dysfunction and cytochrome alteration/inhibition play an important role in the induction of oxidative stress and alteration of the body chemistry in the development of acute autoimmune diseases and/or sudden allergic reaction, and our patient's case was indeed multifactorial with a genetic and molecular basis. From these facts, there is a possibility for the elimination of the idea that the patient had an allergic reaction for Clopidogrel, or the idea that any of the above-mentioned drugs had any role in altering the cytochrome system or causing a cytochrome mutation/failure. For this reason, it is important to conduct new researches to study the effect of multi-drug therapy alongside genetic alteration/mutation on the human body and to develop the proper treatment methodologies in order to avoid life loss in the future.

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Volume 6 Issue 2 February 2019