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Study of Immune - Endocrine Interference Following A State of Post-Traumatic Stress in Road Accident Victims

[1]Amina. Djouini , [2]Abdelmadjid. Bairi, [3]Leila. Brahimi Djouini , [4]Moncef. Hatem. Atia, [5]Lamine Mezedjri

[1]Department of Biology, faculty of sciences, Badji Mokhtar University, Annaba, Algeria.
[2]Department of Biology, faculty of sciences, Badji Mokhtar University, Annaba, Algeria.
[3]Department of Biology, faculty of sciences, Badji Mokhtar University, Annaba, Algeria
[4]Department of Orthopedic Surgery, Ibn Rochd Hospital,Annaba, Algeria.
[5]Department of Biology, faculty of sciences, 20 August 1955 University,Skikda , Algeria.

ABSTRACT

Exploration of the variation of the neuroendocrine and the immunity systems in men victims' of a road accident. The experiment was performed at the Ibn-Roshd's CHU Emergency Unity of Annaba (Algeria). It has been spread over a period of 24 months(2011-2013) because it was so difficult to keep a control group over the Annabian population the victim's accident were divided in two groups : not real danger (victim1 group), and suffered physical trauma (victim2 group). Our control group was voluntary which they didn't suffer of any traumatism or have road accident during the five years ago. we have measured the plasma cortisol, testosterone and immunoglobuline levels. The blood sample's were token few hours after accident. The traumatism results in lower plasma cortisol levels in victim2 group(P≤0.0001)than in the control and the victim1 groups too. For the testosterone levels, there was no difference between control and the second group. But the levels decreased in the third group. Changes in plasma hormones concentrations can be allowed as to suggest that the victim2 group (P≤0.0001), is the one who has developed the physical characteristics of PDST. Whereas, there was a very significant difference (P≤0.001) in the IgG levels of the two victims group compared to the control one. These data demonstrate that the traffic accident changes in hormones secretion. The high immunosuppression seems to be explained by an overactive HPA system. The response of any patient in front of a traumatism is depending on the nature and intensity (physical assault, natural disaster, accident). When the stress is involved, we know that there is a disturbance of the various neuroendocrine and metabolic systems. We propose that the patient must have more medical attention especially to be better support psychological.

Key words: Stress, PTSD, cortisol, testosterone, immunity, accidents,

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INTRODUCTION

We all use the word "trauma" in everyday language to mean a highly stressful event. There is no clear division between stress, trauma, and adaptation [1].

Thus, a traumatic event or situation creates psychological trauma when it overwhelms the individual's ability to cope, and leaves that person fearing death, annihilation, mutilation, or psychosis [2].

It includes responses to powerful one-time incidents like accidents, natural disasters, crimes, surgeries, deaths, and other violent events. It also includes responses to chronic or repetitive experiences such as child abuse, combat,

urban violence, rape, sexual assault, Vietnam War**,** viol, concentration camps, and wars [3; 4]. So, the survivor can develop PTSD if he has been directly involved in a serious traumatic event like those described.

In other words, trauma is defined by the *experience of the survivor*. Two people could undergo the same noxious event and one person might be traumatized while the other person remained relatively unscathed. It is not possible to make blanket generalizations. The intrusion of the past into the present is one of the main problems confronting the trauma survivor or victim [1].

A number of traumatic events like road accident can elevate the risk of post-traumatic stress disorder (PTSD). It's a very big healthy problem for all the government in the world. It has been found that of those who were in an accident where medical attention was needed; almost 40% developed PTSD [5].

A number of studies are trying to identify risk factors for developing PTSD after traffic accidents. And to try some therapy treatment that may be helpful for someone who was faced to vehicle accident. It is common that, not everyone who experiences a traffic accident develops PTSD.

In Algeria, the majority of survivors or victims didn't consult after a tragic accident, some of them are ignorant of the psychological effects, and other doesn't support the idea of healthy traumatism.

In the World if we don't take early some measures, the traffic accidents could be the third principal causes of maladies and traumatisms in 2020.

A study of *the National Police* showed that the increase in the number of uneven road (road accidents) reported in recent years in Algeria, has caused a large number of human casualties (deaths, serious injuries). *For example, the results for the first three months of 2011 show an upward trend of road accidents. For the first term of 2011, the National Police said that 758 people died in road accidents and 8412 injured. Compared to the first term of 2010, the number of deaths increased by 143 (23.25 %), the wounded of 2138 (34.08 %) and the uneven of 1 248 (34.12 %).*

When the car accident happened, which is a traumatic event; the accident victims have in major cases no opportunity to complete treatments. This is how unresolved trauma leads to post-traumatic stress disorders.

Because of the anxiety that often follows a road accident, it is natural that survivor may want to avoid some situations or experience hesitation at times, such as driving on the highway. An increased heart rate when the patient is faced with reminders of the event is described.

We can say there are more symptoms associated with PTSD after a traffic trauma [5]. So, they are probably many symptoms of PTSD, and very few people have all of them.

Interestingly, studies have not found much support for the influence of specific characteristics of the accident (for example, how severe it was, driver or passenger injured) on the development of PTSD. Instead, there is more support for how one responded to, or perceived, the accident [5].

It's clear, sensory information about the trauma, is given high priority in the mind, and is remembered as something threatening. The chance of developing PTSD goes up if the trauma (degree of the accident) was very severe, chronic.

So, the stress is a reaction of the organism: confronted with danger, it helps this one to cope. Thus, we can say that if the magnitude of the stressful event (also known stressor) does not exceed the capacity of normal response, the body will not suffer the consequences. Conversely, if the resources of that body are overwhelmed (it cannot cope with the amount of stress it must manage), all kinds of problems are likely to occur [6].

Among the psychological and physiological consequences that may suffer a subject facing an exceptional or threatening event, the PTSD state is a common evolutionary mode, disabling, highly complex and tends to become chronic in the absence of clinical identification. There is no right or wrong way to feel after traumatic events. But there are many strategies that can help survivor or victim work through feelings of pain, fear, and grief and regain his emotional equilibrium.

The PTSD is a straight psychological reaction to a situation in which the physical and / or psychological integrity of the patient and / or his entourage has been threatened and / or actually damaged (serious trauma events). The

immediate response to the event must have resulted by an intense fear, a feeling of helplessness or a sense of horror. If a fragile psychological or psychiatric field (depression, anxiety...) may increase the risk of developing PTSD, a traumatic experience can alone reveal a PTSD in people with no history. This kind of medical disorder affects approximately 1 in 10 people. They are among the most common of mental health problems. Especially children and the elderly would be more vulnerable. Fortunately, treatments exist to help people with PTSD, because symptoms can vary. For some people, recovery may be achieved in 6 months; for others, it may take much longer [7].

In addition to PTSD, a number of other psychological problems often are present after a vehicles accident. Mood disturbances are particularly common, with one report indicating that 53% of patients with PTSD have concurrent mood disorders [8]. The presence of chronic pain may be the single most defining characteristic. The pain symptoms be attributed to injuries sustained during their road accident and that the pain symptoms had not responded to standard medical treatment after one month [9].

The scientific literature has been on possible disturbances in the hypothalamic– pituitary–adrenal (HPA) axis. During acute stress the HPA axis is activated; the hypothalamus secretes corticotrophin-releasing hormone (CRH) under the influence of serotonin from the amygdala. Subsequently, CRH stimulates the pituitary to release adrenocorticotropic hormone (ACTH), which results in the production of glucocorticoids (cortisol) in the adrenal cortex. Cortisol serves to stop many metabolic, neuronal defensive and immune reactions. Consequently energy can be mobilized to cope adequately with the stressor [10].

When the stress is punctual, he's positive; a hormone is synthesized called adrenaline. The stress can rich a chronic peak, he changed his effect and will be negative on the body health. Another hormone is synthesized and secreted, the cortisol. On the other hand, mental stress has a negative impact on testosterone secretion. Combining the mental and physical aspects of stress, testosterone can drop to clearly hypogonadal levels [11]. The decrease of testosterone levels under stressful situations is usually not sufficiently answered by the pituitary to compensate for the decrease.

Testosterone has a significant influence on important aspect of a life such as sexuality and social status. Stressful situations had shown a decrease testosterone levels [12]. Stress release, on the contrary, can have an elevating effect on androgen levels. In addition, cortisol levels, as a prominent endocrine marker for physical or mental stress exposure, are elevated significantly in runners in comparison to controls [13].

In depressive studies showed that testosterone secretion as well as mean levels were decreased significantly in patients whereas LH levels do not change. The relationship of major depression to stress becomes evident by the increased baseline activity of the HPA axis in patients with the disease.

Urinary cortical secretion is significantly increased in depressive patients. This phenomenon is also observed in post-traumatic stress disorder, which can lead to depressive states [14, 15]. The effects of depressive illness on androgen levels and vice versa are probably closely related to general stress reactions. It was showed that external administration of testosterone is therefore considered for the treatment of depressive states [15, 16].

The objective of this study is to focus on biological disturbances (cortical and testosterone) and immune (IgG) in the hours following the accident and those in a male population which is more representative of victims of traffic accidents in our country. And in order to give the appearance of indicators of potential problems related to the severity of the consequences of such accidents.

Our study provides this to be very useful, and particularly in the context of public health. This study will give some indicators both on the medical aspect and on psychological disorders in men victims.

MATERIALS AND METHODS

2.1 Biological Material

The sixty (60) men used in this study were aged from 35 to 40 years. Most of them, about forty, have suffered of many physical traumas in a violent traffic accident occurred few hours ago. They were selected when they were at the Ibn Roshd's Emergency CHU of Annaba. The suffered groups were called as victim and were compared to a control one which was composed with 20 individuals (men). This control group doesn't have suffered seriously by any physical or psychological trauma for 5 years ago based on data taken from an epidemic-sociologic schedule after they answered on.

2.1.1 Place of experimentation:
The experiment was performed at the *Ibn-Roshd*'s CHU Emergency Unity of Annaba (Algeria). It has been spread over a period of 24 months because it was so difficult to keep a control group over the Annabian population. All experiments sample were realized during the summer season (June-August), known for its higher rate of traffic accidents period.

2.1.2 - Experimental Lots:
The patients selected for this study were divided in two experimental groups of 20 people each, (n=20). Our selection was based on the violent injury destructiveness related to the road accident, according to the severity of injuries, and after medical advice. The first group is called, victim 1. The second , victim2. The two groups were compared to the control one (healthy men).

Control group (T): Individuals of this group were volunteered for the experiment. They have a psychological balance, and did not suffer any trauma experienced for 5 years ago.

Victim1: Individuals of this group have been considered as not in real danger despite having suffered physical trauma (traffic accident), but requiring a transfer to the Emergency structure, given their minor injuries.

Victim2: Men's in this group have suffered physical trauma (traffic accident), with serious injuries and poor vital prognostic who need immediate transfer to Emergency services.

2.1.3 Blood samples:
The blood was collected in the morning when the victims were admonished to the Emergency Ibn Rushd's Hospital. About 400µl of blood was collected in EDTA tubes under local anesthesia and via pricking an arms vein. The blood was centrifugation for 20 minutes at 3500 r / min.

After immediate centrifugation for 20 minutes at 3500 r / min, the plasma was transferred to an Eppendorf tubes, then was frozen at -14 °C. The plasma has been used to quantify in one way two hormones, cortisol and testosterone. And in the other way to measure IgG levels.

2.2 Dosage Methods:
2.2.1 Determination of cortisol and testosterone concentration:
We used the electro- chemistry-luminescence test (ECLIA) to determinate the plasma levels of cortisol and testosterone hormones. This test is suitable for immune dosages on the Elecsys 1010 [17].

2.2.2 Dosage of immunoglobulin (IgG):
The dosage was performed with a dosage kit specific to immunoglobulin and containing antiserum anti-IgG. The human IgG are immunologic markers of the immune response.

2.3 Analysis of results:
Data are presented as mean ± SEM. Differences in plasma cortisol and testosterone levels among groups were tested using ANOVA; followed by Dunnett multiple comparison tests, comparing levels of hormones and immune globulins with the control.

RESULTS

3.1 Variations of plasma cortisol concentration in a man after a road accident:
Figure 1 show the variation of plasma cortisol levels in males .Data are expressed as mean ± standard deviation.

The data analyses showed a very high significant difference ($P \leq 0.0001$) among the three groups. Plasma cortisol levels in males in victim 1 group showed significant changes ($P \leq 0.05$) compared with control group. But in victim2 group, plasma cortisol levels was low (102.83 ± 3.52 nmol/l) than those in the control and victim1 groups ($P \leq 0.0001$) (Fig.1).there was a very significant difference in the control group compared to the two the victims groups($P \leq 0.0001$).

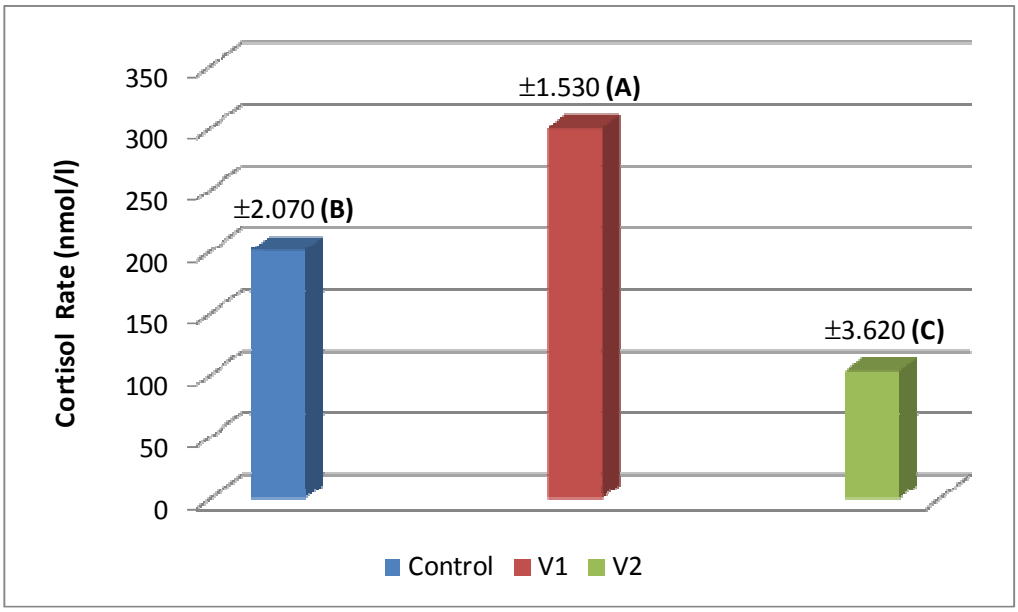

Fig.1: Changes in plasma cortisol levels (means ±SEM) in males not in real danger (victim1) and in males suffered physical trauma (victim2) after a road accident. Significant difference,* * *P≤0.0001;
A (P≤0.05);B(P≤0.001);C(P≤0.0001).

3.2 Variations of plasma testosterone concentration in a man after a road accident:
Figure 2 shows the variation of plasma testosterone concentrations in males after. Data are expressed as mean ± standard deviation.

The data ANOVA analyses showed a very high significant difference (P≤0.0001) among the three groups. In males victim's 1 group there is very significant difference in plasma testosterone concentrations after traffic's accident. Testosterone concentrations drops high significantly in male of the third group (9.38 ± 0.27 nmol / l) (Tab.2; Fig.2).

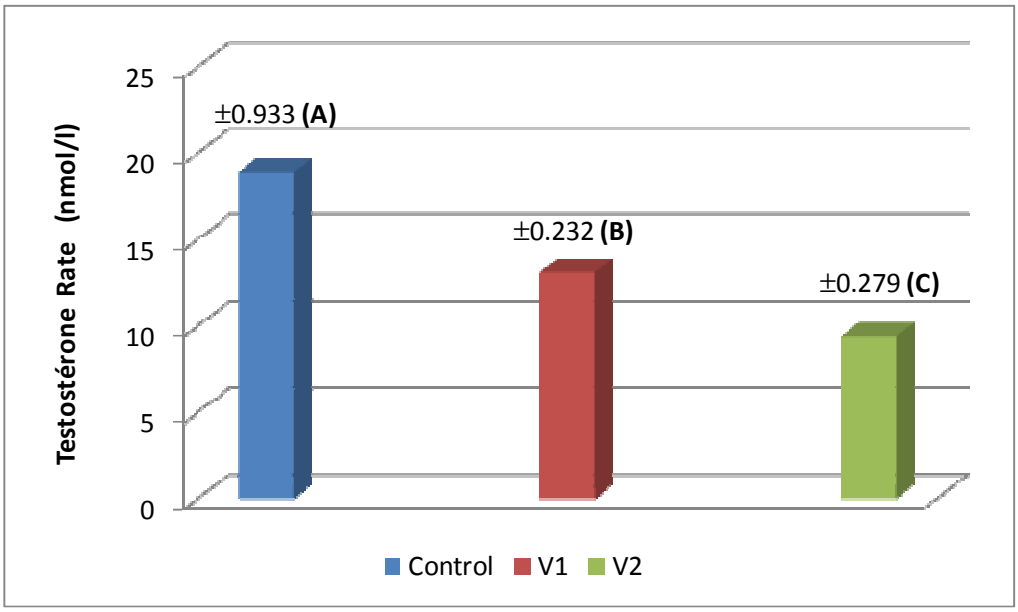

Fig.2: Changes in plasma Testosterone concentrations (means ±SEM) in male's not in real danger (victim1) and in males suffered physical trauma (victim2) after road accident. Significant difference, ,* * *P≤0.0001;
A (P≤0.05);B(P≤0.001);C(P≤0.0001).

3.3 Variation of humoral immune parameters (IgG) (g / l) in a man after a road accident:
Figure 3 show the variation of humoral immune parameters in males after road accident. Data are expressed as mean ± standard deviation.

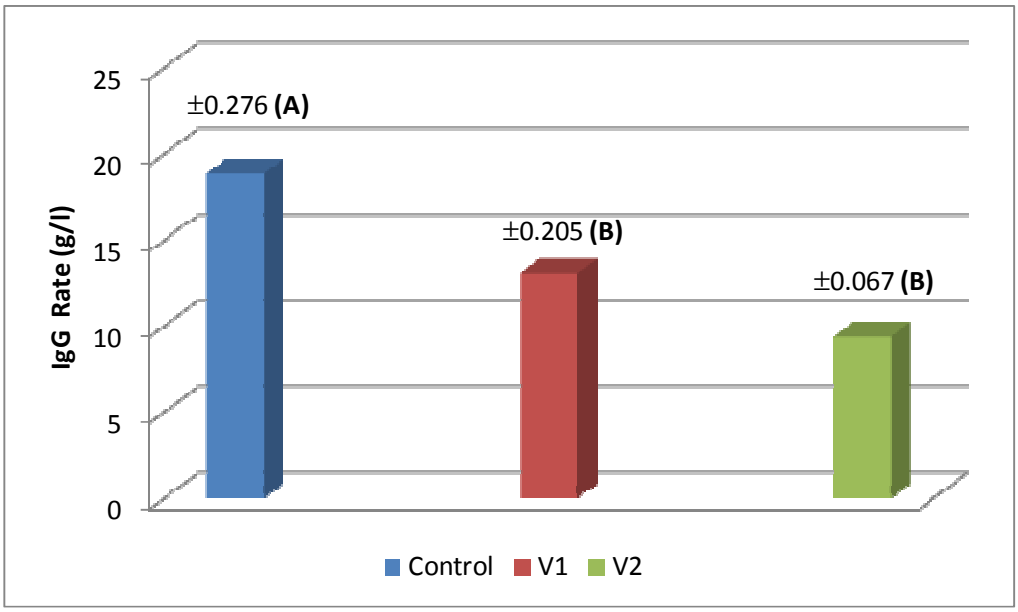

Fig.3: Variation of the rate of immune globulins IgG (g / l) (means ±SEM) in males not in real danger (victim1) and in males suffered physical trauma (victim2) after road accident,* * *P≤0.0001;A (P≤0.05);B(P≤0.001).

Figure 3 shows a very higher significant difference immunosuppressant in humoral levels among the three groups. IgG levels were very significantly lower P≤0.001) in victim1 males (9.91 ± 0.20 g / l) and victim2 males respectively (9.89 ± 0.06 g / l) compared with controls (12.29 ± 0.27 g / l). the control ‘s levels were significantly higher(P≤0.05) (Fig.2).

DISCUSSION

The relationship between the post- traumatic stress (PDST) and kind of traumatisms is well established. The commonest patterns are for stress and traumatism to be mutually exclusive because both stress and traumatism are linked to develop negative responses. PTSD is an anxiety disorder that often follows a traumatic event involving actual or threatened death, serious injury, or threat to the physical integrity of oneself or others [18]. It is prudent to screen victims who report a serious road accident for PTSD. In the case of road accident survivors, easy to administer self-report screening tools may help to identify individuals in both psychological and medical settings who are suffering serious psychological squeals of a road accident [9].

The data demonstrate that both cortisol and testosterone concentrations were affected after a traumatism in man. As other agent of stress, road accident caused damages in human body. For example, in 2004 just fewer than 6.2 million traffic accidents were reported to police departments in the United States resulting in approximately 2.8 million injuries (9). The stress also called stressor, when it affects the reactions is imminent. There will be a cascade of neural and hormonal responses which trigger survival mechanism that represents the flight response – aggression [19].

In the present study, the increase in cortisol levels especially in the second group, allow as to qualified it as ‘’stressed’’ males. Low cortisol is observed in the third group. This one may it the PDST subjects compared with controls. Clearly, the cortisol itself is a marker which can help to determinate if the body developed the signals of the PDST.

The mechanism by which the stress actives the corticotrophin axis is known. Firstly, there is a higher secretion of CRF, ACTH, and cortisol. Secondarily by the adrenal glands which become enlarged [20]. The corticotrophin axis or hypothalamic-pituitary -adrenal (HHS) is a neuroendocrine system with a cascade of negative feedback loop. It leads to the synthesis and secretion of glucocorticoids. Faced with a strong emotional event, the HHS (HPA) axis is activated resulting in the production of cortisol.

It’s clears that a traumatic event could increase this physiologic phenomenon. The glucocorticoids are highly lipophilic substances and therefore, they have the ability to pass easily the blood -brain barrier.

Physiologically, there are both many glucocorticoid and mineralocorticoids receptors present in the hypothalamus and the hippocampal regions. These two structures are implicated in the control of our humor and the capacity to feel pleaser. These receptors are very sensitive to the level and the time of corticoids activation in the body [13]. We can suggest that these receptors activities may change the behavior when the traumatisms target the HPA axis. It was also reported a decrease in hippocampal volume in individuals developed PTSD [13].

Moreover, in patient with PDST, it founds in imagery, atrophy at the hippocampal level and memory deficits. Starkman [9] in 2010 confronts his observations in patients with Cushing's, with high cortisol levels, and he finds the same elements (ie memory impairment and hippocampal atrophy) [21, 22].

In number of studies, it has been shown that patients with PDST have variations in their negative feedback. So, the dexamethasone test (glucocorticoid receptor agonist) induced a strong inhibition of the HHS (HPA) axis (hypersensitivity of glucocorticoid receptors) [23]. On the other hand, a lower basal cortisol levels are found in this type of patients. On the contrary, when stimulated the axis, the cortisol concentration is much higher [24].

The HHS axis is in patients with PDST, not hypoactive but hyper-reactive [25] and the hippocampal neurons become more vulnerable. It's clear that the trauma may be a risk factor for development a PDST [23, 25].

In men who have assisted to a road accident as conductor or passenger or just crossing the road, the level of the future traumatism is linked with the nature (violence, surprise, life-threatening) and the degree of the accident.

Our study demonstrated that man victims developed either stress or traumatism. We can suggest that significant decreasing testosterone is a cause of stress. It is known that the corticotrophin axis acts on the gonadotropin axis. The testosterone which is a steroid hormone (derived from a sterol) is secreted in man by Leydig cells of the testis under the stimulation of pituitary hormone, the luteinizing hormone (LH).

The testosterone circulates in the blood plasma, bound to proteins, especially the Sex Binding Protein (SBP). Testosterone secretion begins during life in utero, and then stops almost completely after birth again during puberty. Testosterone is necessary for spermatogenesis (sperm production) and genital development, therefore fertility.

These data suggest that the plasma testosterone concentration in victim2 group tend to suppose that they are the PDST patient comparatively to control group and the victim1 group. The levels are lower than in the second group. And like in our cortisol results, the same group shows a decrease in hormones stress levels. Stress, act on spermatogenesis by hormonal or neural pathways. Hormonal pathway leads to a decrease in production of LHRH, a drop of LH receptors on Leydig cells and a decrease in enzyme activity 17α hydroxylase. Thus, in case of significant and prolonged stress, testosterone decreases and spermatogenesis may be affected [26].

Chronic stress decreases the secretion of testosterone, an effect that is associated with a decrease in plasma gonadotropin levels. Stress and trauma have a suppressive effect on the production of testosterone. Indeed, interest rates fell by 90% in men undergoing castration on advanced prostate cancer [27].

The role of testosterone in the control human behavior is well established. There is an association between plasma testosterone and perceived aggressive behavior. This makes an interest of hormonal variations in humans facing a traumatic and non-traumatic event [28, 29].

At present, the majority of clinical studies on the pathology and stress relationship are based on a descriptive epidemiological approach. On the one hand, it is essential that neurobiologists, immunologists, psychiatrists and psychologists work together to develop animal models and the implementation of longitudinal studies. On the other hand, this relationship can promote understanding the mechanisms underlying the stress and immune disease link.

Ultimately, these studies will be able to answer the question: Is stress an important factor in the genesis of certain diseases? If so, how can it resolve the stress-disease mechanisms?

As stress is both psychological (trauma, emotion, anger, annoyance, sleep, overwork, depression, etc...) and biological events (surgery, temperature variations), it may cause variations in the body and can cause more or less disturbances as a serious depression of the immune system.

Aggression, stimulation, shock, stress voltage, shock, emotion, imbalance, depression, illness, malaise, are all French words that could better inform us that the only English word is stress [30]. There is now a literature «meaningful " showing that psychological stress can create a decrease in cellular immune response. The same

results are obtained in the present study, who in the two victim groups, we can observe a significant decrease in the IgG levels. We recorded an immunosuppression, compared with the lot of male control subjects.

The effect of road accident on the physiological behavior must be more investigated maybe with large samples. Four major systems are involved to control hormones levels and immunity. These systems are: nervous, central, autonomous (sympathetic and parasympathetic) neuroendocrine and immune systems. The four systems interact mutually with stress and its various manifestations. These relationships are at the local level in some "organs" as the skin, heart and intestine [31].

CONCLUSION

In terms of number of victims of road accidents, Algeria has the dubious distinction of being ranked first at the scale of the Arab world, and the fourth worldwide,

Trauma due to traffic accidents is a huge public health problem,

Trauma is a set of local or systemic manifestations caused by a violent action on the body

Physical trauma injures the body but can also, as the psychic trauma, attain the mental and cause behavioral and psychological disturbances due to violent emotional shock. Many victims or witnesses of a road accident trauma often develop trauma. If symptoms persist more than a month, we talk about post- traumatic stress disorder (PTSD). Disorder PTSD is a psychological consecutive reaction to a situation in which the physical and / or psychological patient integrity has been threatened and / or actually damaged (including serious accidents, violent death, rape, assault, serious illness, war, terrorist attack).

Our results show that after the hours following the accident a significant decrease in levels of cortical and testosterone and serum immunoglobulin is recorded for the lot (V2): men with serious physical injuries as a result of accident, which may suggest the development of PTSD in individuals of that lot.

The interest of this work is that through bioassays and more of a psychological assessment established because of road accident, find a way to identify those likely to develop PTSD so that care is quickly put in place to limit the impact of this disease on the family or social life, work of the victims.

It is interesting to do:
- A study with a larger sample size and in longer term (longer time) to better specify the causes of a of post-traumatic stress state and characterize the environmental, sociological and familial factors for installation in a given population.

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