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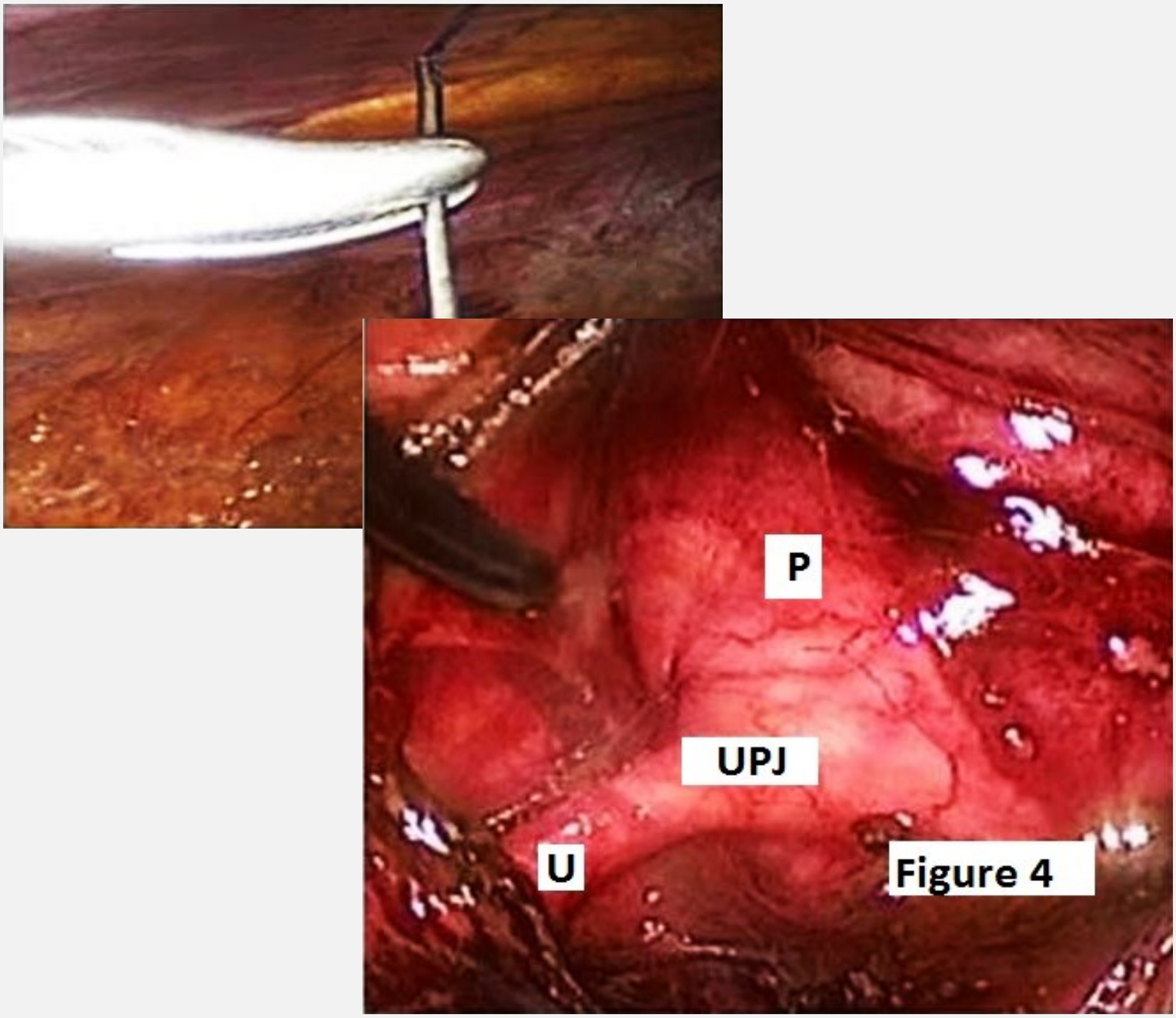

High Lights

- Effects of radio-frequency radiation on the permeability of blood-brain barrier
- The Laparoscopic Management of the Ureteropelvic Junction Obstruction
- Zellweger syndrome accompanied by hypertrophic cardiomyopathy

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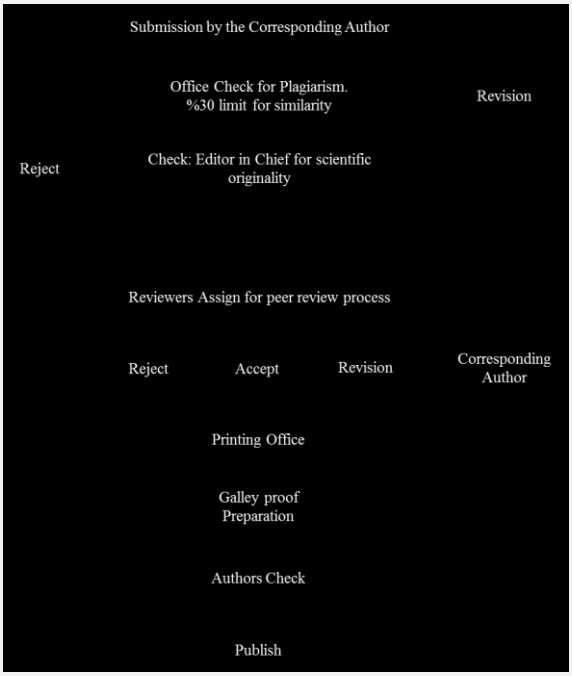

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Review Article

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Effects of radio-frequency radiation on the permeability of blood-brain barrier

Bahriye Sirav[1*], Nesrin Seyhan[1]

Abstract

Health concerns have been a raised after the enormous increase in the use of mobile phones and related base stations throughout the world. In spite of extensive increase in the studies of biological effects of mobile phone radiations with in last decades, little is known about the effect of long term exposure. In this present report, we summarized a review of the literature on the effects of radio-frequency radiation exposure on the permeability of blood-brain barrier. Gazi University Biophysics group have earlier shown that the electromagnetic radiation emitted by mobile phones – also called radio-frequency radiation - alters the permeability of the blood–brain barrier, GSM like modulated fields were found to be more effective than continuous-wave fields. This paper will review some evidence that demonstrates the existence of non-thermal effects and the exposure complexities that must be considered and understood to provide appropriate, more thorough evaluation and guidance for future studies and for assessment of potential health consequences

Key Words: Permeability; Blood brain barrier; Radio Frequency Radiation; Mobile Phones

Introduction

For many years there has been a discussion among the general public regarding the biological effects of radio-frequency radiation (RFR) on the human organism. The mobile phone induced effects on the permeability of blood-brain barrier (BBB) is one of the main topics of importance for the whole society today. Electromagnetic spectrum (Figure 1) covers a broad frequency range; static electric and magnetic fields, low-frequency electric and magnetic fields and high-frequency electromagnetic fields that is also called radio-frequency radiation, infrared radiation (IR), visible light, ultraviolet radiation (UV), X-rays and Gamma Rays which includes 1022 Hz frequencies. The upper radiofrequency range (GHz range- tens/hundreds of 109 Hz) includes microwaves. RFR does not have sufficient energy to produce ionization. It is universally accepted that RFR can cause tissue heating (thermal effects) and extremely low-frequency (ELF) fields, e.g., 50 and 60 Hz, can cause electrical current flows that shock and even damage or destroy tissues (12). These factors alone are the underlying bases for present electromagnetic field exposure standards. The article reviews current research on biological effects of RFR on the permeability of blood-brain barrier..

Overview

Today more than half of the world's population owns mobile phones. For 2017, the number of mobile phone users is forecast to reach 4.77 billion. Lifelong exposure to the radio frequency radiations (RFR) from mobile phones, with start already at a young age, is becoming increasingly among the new generations of mobile phone users. The mobile phones are held in close proximity to the head, or with in a meter of the head when hands-free kits are used. The emitted radio-frequency radiation have been shown to have many effects upon the brain; e.g. alterations of cognitive functions (1), gene expression alterations in cerebellum (2), cortex and hippocampus (3), changes of neurotransmitter levels such as decrease of cholinergic activity (4), and effect on brain waves as determined by electroencephalography - EEG (5). Epidemiological studies also indicate that long term exposure increases the risk of not only acoustic neuroma (6), but also malignant glioblastoma multiform (7) for mobile phone use longer than 10 years. The WHO (World Health Organization) / International Agency for Research on Cancer (IARC) has classified RFR as possibly carcinogenic to humans (2B) based on the increased risk for glioma, a malignant type of brain cancer associated with wireless phone use (8).

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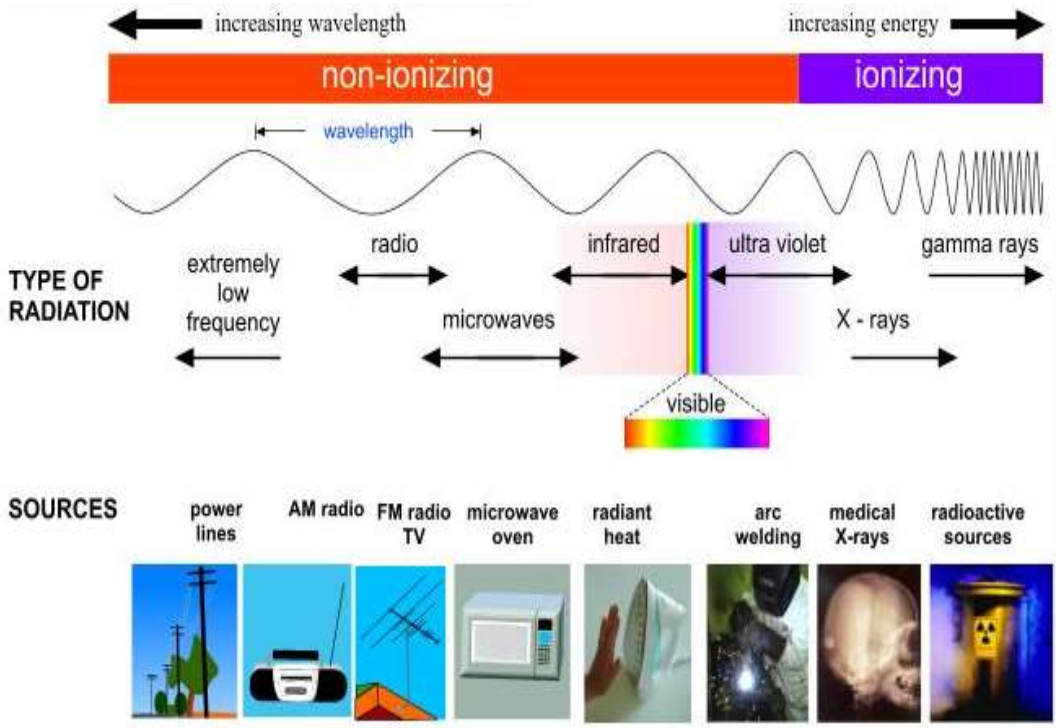

Figure 1. Electromagnetic Spectrum

IARC working group discussed one study of past mobile phone use (up to the year 2004), this study showed a 40 % increased risk of gliomas in the highest category of heavy mobile phone users (Reported average: 30 minutes per day over a 10 year period).

It has been shown that RFR leads to increase in the permeability of the blood–brain barrier (BBB) (Figure 2) (9-10).

The BBB is a hydrophobic barrier, formed by vascular endothelial cells of the capillaries in the brain, with tight junctions between these endothelial cells (11). It protects the mammalian brain from potentially harmful compounds in the blood. Perivascular structures such as astrocytes and pericytes as well as a bi-layered basal membrane also help maintaining the BBB. In the functioning BBB, the membrane properties control the bidirectional exchange between the general circulation and the central nervous system - CNS. Water, most lipid-soluble molecules, oxygen and carbon dioxide can diffuse from the blood to the nerve cells. The barrier is slightly permeable to ions such as sodium, potassium and chloride, but large molecules, such as proteins and most water-soluble chemicals pass poorly. However, when this barrier is damaged, in conditions such as tumors or infections, the normally excluded molecules can pass through, possibly bringing toxic molecules out into the brain tissue.

The selective permeability is disrupted temporally in cases of epileptic seizures (10). The result of this can be cerebral edema, increased intracranial pressure and irreversible brain damage. Also, toxic substances from the blood circulation now reach out to the neurons. Even transient openings of the BBB can lead to permanent tissue damage (11).

Many national and international exposure standards for RFR exposure from the use of mobile phone, related base stations, radars, other wireless devices, Wi-Fi systems etc. are ultimately based on the production of heat particularly in regions of the head, that is, thermal effects. The recent recommendations for limits of exposure to the general public for RFR (12) are set in order to avoid thermal effects upon the brain parenchyma. There are some reports that discuss the existence of non-thermal effects, and include provisions for reduced maximum-allowable limits should certain radiation characteristics occur during the exposure.

In the previous 1970s, when the radiation from radars and microwave ovens were considered to be possible health threats, the first studies on the microwave (MW) (in the GHz regions of RFR spectrum) effects upon the BBB were reported. Increased leakage of fluorescein after 30 min of pulsed and CW exposure (13) and passage of ^{14}C-mannitol, inulin and dextran at very low energy levels (14) were reported.

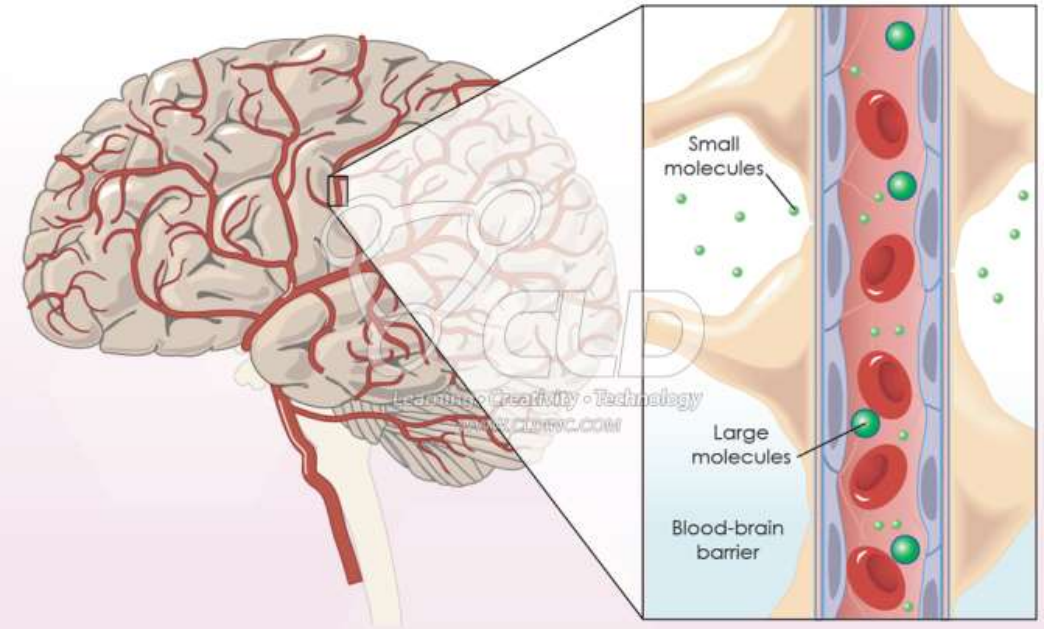

Figure 2: General structure of blood-brain barrier

The permeation of mannitol was found to be a definite function of exposure parameters such as power density, pulse width, and the number of pulses per second. Also, the BBB permeability depended on the time between RFR exposure and the sacrifice of the animals, with more pronounced effects seen in the animals sacrificed earlier after the RFR exposure. However, these results were not found in some replication studies (15). No induced BBB effects, was reported by Ward et al. (16) after exposure of rats to CWs at 2450 MHz; Ward and Ali (17) investigated the permeability of blood-brain barrier to high and low molecular weight compounds under CW and pulsed-RFR. They exposed RFR on animals at 0.1 W/kg SAR values and they found no change in uptake of either sucrose or inulin as compared with those of sham exposed animals. Gruenau et al. (18) exposed animals to pulsed or CW waves at 1.8 GHz (including totally 31 rats) and found no effect about these exposures. On the other hand, Albert and Kerns (19) observed RFR induced BBB permeability after exposure at 2450 MHz CWs, with an increase in the number of pinocytotic vesicles among the irradiated animals. However, after a recovery time of 1–2 h, the permeation was not detectable anymore.

In our previous studies we have seen that non-thermal RF fields cause significantly increased leakage through the BBB of exposed rats sacrificed immediately after the RFR exposure, as compared to sham exposed animals (20-22). We have used 900 MHz and 1800 MHz, continuous wave and global system for mobile communications (GSM) modulated RFR and found increased permeability of blood-brain barrier of both female and male rats in non-thermal levels. Eberhardt et al (2008) have shown that two hours of exposure to the radiation from a GSM phone at 915 MHz, at non-thermal specific absorption rates (SAR) values of 0.12 mW/kg, 12 mW/kg and 120 mW/kg, gives rise to focal albumin extravasation and albumin uptake into neurons also 14 days after exposure (23). Significant neuronal damage is present 28 days and 50 days after exposure (24), but not after 14 days. BBB permeability is also increased in connection to mobile phone exposure in experiments from other laboratories (25-26). The effects of exposure to MRI related fields upon the BBB permeability were also investigated. MRI includes an exposure to a high-intensity static field, a RF field and a time-varying magnetic field. Shivers et al. (27) observed that the EMF exposure of MRI procedure resulted in a temporarily increased BBB permeability in the brains of rats. A vesicle-mediated transport of horseradish peroxidase (HRP) took place through transendothelial channels. Replications of the initial findings by Shivers et al. (27) were made by Garber et al. (28), whereas Adzamli et al. (29) and Preston et al. (30) could not confirm the findings. In 1990, quantitative support of the findings by Shivers et al. (20) was presented by the same group.

The BBB permeability to DTPA (diethylenetriameninepentaacetic acid) increased in rats exposed to the MRI. A suggested mechanism explaining the increased permeability was a stimulation of endocytosis, made possible through the time-varying magnetic fields. Salford's studies repeated the findings of the Shiver & Prato group; BBB permeability to albumin was increased after

exposure to MRI radiation. The most significant effect was observed after exposure to the RF part of the MRI. There are also studies which demonstrated no BBB alterations under mobile phone exposure or MRI exposure (31-32).

Salford et al. found an increased BBB permeability immediately after 2 h of mobile phone exposure (33), and also after 14 days and 50 days. Repetitions of their findings of increased BBB permeability after mobile phone exposure have been made (34). Four hours of 900 MHz exposure at brain (0.3 to 7.5 W/kg) resulted in significantly increased albumin extravasation both at the SAR-value of 7.5 W/kg, which is a thermal effect, but extravasation was seen also at 0.3 W/kg and 1.3 W/kg (35). Albumin extravasation was also seen in rats exposed for 2 h to GSM liked modulated 900 MHz at non-thermal SAR-values of 0.12, 0.5 and 2 W/kg using fluorescein-labelled proteins. A marked BBB permeabilization was observed at SAR of 2 W/kg, permeabilization was also present around intracranial blood vessels at the lower SAR-value of 0.5 W/kg. However, the extravasation at 0.5 W/kg was seen at a lesser extent as compared to that seen at 2 W/kg. Finnie et al. (36) exposed mice for 1 h daily to RFR with SAR value of 4 W/kg, which is above the ICNIRP limit (12).

In a further study by Finnie et al. (37) 207 mice were exposed for 104 weeks at SAR-values of 0.25–4 W/kg. In both Finnie's studies, there was no effect on the BBB permeability. The same group also reported that the immature BBB was insensitive to mobile phone exposure, seen after GSM- 900 radiation exposure of pregnant mice from day 1 to day 19 of gestation (SAR of 4 W/kg, exposure for 60 min daily). No increased albumin extravasation was seen in the new-born mice immediately after parturition. Kumlin et al. (38) confirmed that 900 MHz radiation have no effect on the BBB permeability of young rats. In vitro models have been increasingly applied to investigate the BBB in last years; in one of these, it was shown that 1.8 GHz exposure increase the permeability to sucrose (39). After modifications of the BBB model to one with higher tightness, however, the same group could not replicate their initial findings (40). They concluded that their in vitro BBB model also did not alter its tightness or transport behavior under the exposure of RFR emitted like 3G mobile phones (41).

There are also some reports that investigated the neuronal damage in connection to mobile phone exposure. Eberhardt et al. have evaluated the occurrence of neuronal damage in animals surviving a longer period after the exposure. This neuronal damage is seen as condensed dark neurons. Dark neurons have been proposed to have three main characteristics (42): (a) irregular cellular outlines, (b) increased chromatin density in the nucleus and cytoplasm and (c) intensely and homogenously stained nucleus. The neuronal damage was significantly increased in the exposed rats as compared to the sham exposed controls twenty-eight days after 2 h of mobile phone exposure (23). There was also an increased occurrence of neuronal damage 50 days after the same kind of mobile phone exposure. In these studies, normal neurons have been shown to have increased uptake of albumin. In previous studies of this group, damaged neurons were seen in all locations, intermingled with normal neurons especially in the cortex, hippocampus and basal ganglia. The damaged neurons were often shrunken and dark staining, homogenized with loss of discernable internal cell structures. Dark neurons are reported in clinical and experimental neuropathology from living tissues, but not in autopsy material unless the post-mortem period is short.

This could indicate that the formation of dark neurons is an active process that requires living neurons and that these cells must be reasonably intact (43). Dark neurons occur not only after GSM exposure but also in connection to experimental ischemia, hypoglycemia (44) and epilepsy (45). A pharmacologic origin, such as depolarization related to tissue glutamate release in injury, could explain the pathogenetic mechanism for dark neurons in these cases, rather than the pressure-derived mechanical origin. The formation of dark neurons can be prevented using pharmacologic forms of glutamate antagonism (42). Ilhan et al. have also reported dark neurons in connection to RFR exposure of rats for 7 days, 1 h daily (46). An increase of oxidative damage was also seen in the exposed rats as a significant increase in malondialdehyde (MDA) (an index for lipid peroxidation), nitric oxide (NO) levels, brain xanthine oxidase (XO) and adenosine deaminase (ADA) activities, as compared to the controls. The RFR induced increments of XO, ADA, MDA and NO were prevented with treatment of the anti-oxidant Gingko biloba. The anti-oxidant activity of Gingko biloba is attributed to its flavinoid glycosides, which are the active compounds in the leaves. The action of these flavinoids is to destroy free radicals, such as NO and lipid peroxide radicals. Also the formation of dark neurons was reported to be prevented when the rats had been treated with Gingko biloba.

It has been suggested that BBB leakage is the major reason for nerve cell injury, such as dark neurons in stroke-prone spontaneously hypertensive rats (47). Albumin leaks into the brain and neuronal degeneration is seen in areas with BBB disruption in several circumstances: after intra-carotid infusion of hyperosmolar solutions in rats; in the stroke prone hypertensive rat (48). The linkage between albumin extravasation over the BBB and neural damage might be a potentiating effect of albumin upon the glutamate-mediated neurotoxicity (11). Indeed, both albumin and glutamate induced lesions have the same histopathological appearance with invasion of

macrophages and absence of neuronal cell bodies and axons in the lesion areas (49). The glutamate itself can also increase the BBB opening (50), leading to further albumin extravasation out into the brain parenchyma.

Conclusion

Scientific literature on the effects of RFR on blood-brain barrier is reviewed. The controversy about potential health hazards associated with the exposure to RFR has been recently stimulated by the increasing use of mobile phones and related RFR sources. Attention has focused here on non-thermal effects of low-level RFR, which does not lead to a heating of tissue. At the present level of knowledge, there is no final comment that can be drawn from the available data concerning potential health hazards. Although there seem to be some biological effects, these cannot provide pure evidence for any adverse health consequences. However, further research is needed for a better understanding of the interaction between RFR and biological effects. In contrast to low-frequency fields, exposure to high-frequency non-ionizing radiation i.e. RFR can lead to significant absorption of energy and temperature increases, depending on the radiation intensity. Safety guidelines recommend upper intensity limits to prevent significant temperature rises. There is increasing evidence that weak RFR, at intensities well below those necessary to cause any significant heating, can also induce biological effects. Attention is now focused on these direct non-thermal effects of low-intensity RFR not mediated by heating of tissue. This holds particularly for the controversy regarding health consequences of the new communication technologies. Although there are an increasing number of reports about biological effects induced by weak RFR, there is still a great lack of available data, especially related with human beings. An important drawback is that the fundamental mechanisms of the interaction with biological systems are not yet understood in detail. Finally, efforts have to be made to elucidate the fundamental mechanisms underlying the interaction of RFR and the central nervous system on the neuronal level. Whereas the effects of high levels of RFR leading to tissue heating are basically understood, there is still a great lack of knowledge regarding the non-thermal effects of low intensity radiation.

Positive findings must be replicated by independent research groups, and interpretation of results must not be distorted due to potential conflicts of interests, because of funding administered by the communication industry or influences of specific interest groups. On the other hand, although negative findings do not necessarily confirm the absence of a potential biological effect, an accumulation of well-performed studies producing negative results will provide increasing confidence regarding the safe use of mobile phones.

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Atherosclerotic and metabolic effects of hypothyroidism due to chronic thyroiditis

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Abstract

Hypothyroidism is the condition of decreased hormone production to provide the needs of peripheral tissues. Clinical symptoms may vary depending on patient's age, disease duration and thyroid hormone levels. Thyroid hormones are important determinants of basal metabolic rate and thyroid hormone status have a strong effect on different metabolic pathways (protein, carbohydrate, lipid) and atherosclerotic pathogenetic mechanisms.

This review focuses on metabolic and atherosclerotic effects of hypothyroidism due to chronic (hashimoto) thyroiditis.

Key Words: Hypothyroidism, basal metabolism, body composition, atherosclerosis

Introduction

Hypothyroidism refers to reduced hormone production in the thyroid gland and the inability to produce thyroid hormones that provides the needs for peripheral tissues. Primary hypothyroidism accounts for more than 95% of all hypothyroid cases. Primary hypothyroidism is characterized by elevated serum TSH levels and low levels of free serum thyroxine (fT4), and this phenomenon is also called overt hypothyroidism (1).

According to population studies, the prevalence of overt hypothyroidism varies from 0.1 to 2% (2). Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of primary hypothyroidism in regions of the world with sufficient iodine. It is characterized by cellular and antibody-associated damage in the thyroid tissue. Cytotoxic T-cells may cause direct damage in thyrocytes. Furthermore, antibodies may develop in the serum against thyroglobulin (Anti-Tg), against thyroid peroxidase (thyroid microsomal antigen) (Anti-TPO) or against thyroid sodium/iodine transporter in 90% of patients with chronic autoimmune thyroiditis (3).

Clinical symptoms may vary depending on patient's age, disease duration and thyroid hormone levels. The standard treatment of hypothyroidism is hormone replacement therapy with synthetic thyroxine hormone (LT4). LT4 need varies depending on severity of disease as well as lean body mass and total body weight of patients.

Thyroid hormone statuses of a patient have a strong effect on different metabolic pathways and atherosclerotic pathogenic mechanisms.

A PubMed search was performed using the terms "hypothyroidism" AND "basal metabolism, body composition, protein metabolism, carbohydrate metabolism, lipid metabolism and atherosclerosis". The titles were scanned manually and articles of interest regarding the metabolic and atherosclerotic effects of hypothyroidism were reviewed.

The effect of hypothyroidism on basal metabolism

Thyroid gland produces the thyroxine hormone with essentially low biological activity (3, 3', 5, 5'-tetraiodothyronine or T4). At intracellular level, the iodine in the outer ring is removed by type 1 deiodinase (D1) or type 2 deiodinase (D2), forming the 3, 3', 5 triiodothyronine (T3) which binds to thyroid hormone receptor with a 100-fold increased affinity compared to T4 (1).

Classically, thyroid hormones are known to exert their effect on energy homeostasis through peripheral tissues. This effect occurs through the metabolically active tissues such as liver, white and brown adipose tissue, heart and skeletal muscle. Brown adipose tissue shows paravertebral and perirenal distribution in adults and accounts for 20% of energy consumption. Thyroid hormones induce the lipolysis stimulating effect of norepinephrine in brown adipose tissue and also increase UCP (uncoupling protein) expression,

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thereby increasing the mitochondrial heat generation (thermogenesis) (4).

The norepinephrine from sympathetic nervous system binds to β3 adenoreceptors in brown adipose tissue and increases cAMP levels, thereby activating protein kinase A and hormone-sensitive lipase, allowing lipolysis and leading to release of free fatty acids from triglycerides. Free fatty acids (FFA) are activated to acyl-CoA by acyl-CoA synthetase and transported to mitochondria via carnitine palmitoyltransferase 1a (CPT1a). β-oxidation of the acyl-CoAs from FFA occurs in mitochondria. This results in increased UCP1 synthesis, which provides mitochondrial heat generation. Uncoupling proteins stop ATP (adenosine triphosphate) production, causing the energy in nutrients to be released as heat only. UCP1 is an uncoupling protein found only in brown adipose tissue, and thyroid hormones are known to increase UCP1 gene expression. UCP2 and UCP3 are the other uncoupling proteins associated with metabolic and thermogenic effect of thyroid hormones found in muscle, fat and other tissues. Thyroid hormones increase the effect of norepinephrine (NE) in this pathway and also induce UCP1 gene expression, leading to increased uncoupling proteins and thereby increasing mitochondrial heat generation (4). Uncoupling protein-2 is another uncoupling protein which regulates the oxidation pathway. Decreased UCP2 mRNA expression has been shown in periumbilical subcutaneous adipose tissue biopsy in patients with hypothyroidism (5).

Another pathway related to the peripheral effect of thyroid hormones on thermogenesis (heat generation through physiological process) is the pathway associated with bile acids. The discovery that bile acids induce local thyroid hormones by activating type 2 deiodinase has led to demonstrating that thyroid hormones are effective in the thermogenesis increased through bile acids during the post-prandial period (6).

Recently, it has been understood that the effect of thyroid hormones on energy homeostasis does not occur only through peripheral tissues but also centrally through the nuclei in hypothalamus (arcuate, paraventricular and ventromedial). In hypothyroidism, basal metabolic rate (BMR) is thought to decrease owing to the effect on hypothalamic nuclei via the central route and the reduced thermogenic effect on peripheral tissues. Reduced thermogenesis clinically presents as cold intolerance in patients and contributes to storing energy (4).

The effect of hypothyroidism on body weight, body mass index and body composition

Thyroid hormones are important determinants of BMR. Hypothyroidism is associated with decelerated metabolic functions. Patients with hypothyroidism are known to have increased body weight. However, there are contradictory publications regarding the primary factor responsible for this increase. Serum TSH levels are reported to exhibit a positive correlation with body eight and body mass index (BMI) (7-10). While some publications report a positive correlation between serum TSH levels and increased adiposity, some others claim no such association (9). In normal range, only elevated TSH levels have been reported to be associated with increased visceral adipose tissue measured by ultrasonography (11). Publications report different results regarding the changes in body weight and composition following treatment for hypothyroidism. A study reported weight reduction at 6 months after treatment in hypothyroid patients receiving replacement therapy, although the patients returned to their pre-treatment body weight at 24 months (12). Another study reported that correcting hypothyroidism did not lead to any changes in body composition evaluated by DEXA (13). A prospective study where patients with hypothyroidism receiving replacement therapy were followed for 12 months showed statistically significant weight reduction after treatment; however, the weight reduction was shown to be from lean body mass and not from adipose tissue (14). A study which evaluated body composition by DEXA before and after LT4 therapy in patients with hypothyroidism demonstrated significantly decreased BMI and significantly increased adipose tissue while soft tissue mass declined when euthyrodism was achieved with LT4 (5). Another study with DEXA showed weight gain in hypothyroidism and weight reduction after treatment, although the primary factor responsible for the reduction was lean body mass (15).

The effect of hypothyroidism on protein metabolism

Hypothyroidism has complex effects on protein metabolism. Overall, protein synthesis and degradation declines; however, patients with hypothyroidism remain at a positive nitrogen balance. Increased total modifiable albumin pool is seen in myxedema (16). Albumin is distributed to a broad volume, leading to increased capillary wall permeability. Increased glycosaminoglycan synthesis is observed (17). Extracellular protein mobilization occurs after treatment in patients with hypothyroidism, causing a temporarily negative nitrogen balance (18). Urinary excretion of potassium, phosphorus and nitrogen increases in late stage. This suggests that cellular proteins are also metabolized (19).

The effect of hypothyroidism on carbohydrate metabolism

Intestinal glucose absorption is slower than normal in hypothyroidism. Studies comparing fasting plasma glucose and fasting insulin levels versus controls have often reported normal results (20, 21). However, some

studies report the possibility of mildly low glucose levels and mildly high insulin levels (22-24).

The HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index used to measure insulin resistance reflects the insulin resistance at fasting state (particularly at hepatic level). Matsuda index is calculated using the insulin and plasma glucose levels measured during the oral glucose tolerance test and provides insight on insulin sensitivity in peripheral tissues (25). Comparison on HOMA-IR index in patients with hypothyroidism versus euthyroid controls revealed normal results in some studies (20, 21, 26) while other reported increased index in these patients (24, 27). Matsuda index has been reported to decline in hypothyroidism and show positive correlation with serum fT4 levels (21, 24). These studies suggest that while some patients with hypothyroidism may have insulin resistance at fasting state, decreased post-prandial insulin sensitivity is more common among hypothyroid cases. Decreased insulin-mediated glucose transfer has been shown in patients with hypothyroidism due to the disrupted GLUT-4 (glucose transporter-4) translocations in monocyte plasma membranes (24). Post-prandial glucose intake in muscle and adipose tissue has been reported to decrease in patients with hypothyroidism compared to euthyroids (21). Studies with euglycemic hyperinsulinemic clamp test have reported corrected insulin sensitivity in patients with hypothyroidism upon achieving euthyrodism (28).

The effect of hypothyroidism on lipid metabolism

Lipolysis and biosynthesis of fatty acids are decreased in hypothyroidism. Total cholesterol is increased and LDL-C (low density lipoprotein cholesterol) is the main factor responsible for this increase. Decreased T3-dependent gene expression of hepatic LDL-C receptors necessary for LDL-C clearance in the liver is reported to cause elevated LDL-C levels (29). Furthermore, LDL-C oxidability is also increased in hypothyroidism (30).

Increased HDL2 despite stable HDL3 levels in hypothyroidism is associated with the decreased activity of hepatic lipase which normally allows the transformation of CETP (cholesteryl ester transfer protein) and HDL2 to HDL3 (31).

While apolipoprotein B and AI are increased, no change is seen in apolipoprotein AII. In some patients, decreased lipoprotein activity in adipose tissue and therefore reduced triglyceride clearance is responsible for the increased triglyceride levels (31). Greater post-prandial lipemia (defined as more than 80% increase in triglycerides) was observed in patients with hypothyroidism compared to the control group in an oral lipid tolerance test study (37). Free fatty acid concentration is reported to be normal in hypothyroidism; however, some reports indicate increased and some others report decreased concentrations as well (33). While some studies report increased lipoprotein (a) levels in hypothyroidism which declines with treatment, some others have reported no change in lipoprotein (a) levels (34-36).

A study in patients with short-term overt hypothyroidism showed increased total cholesterol and LDL-C levels with no change in small LDL particles, which are more atherogenic; and triglyceride levels were observed to be borderline high while no change in was seen in large VLDL particles, which are also more atherogenic. This study found a shift to large LDL, small VLDL and large HDL particles, which are less atherogenic, despite the increased levels of total cholesterol and LDL in hypothyroidism (37).

The effect of hypothyroidism on renal functions, water and electrolytes

Renal blood flow is decreased in hypothyroidism due to reduced cardiac output and blood volume. Glomerular filtration rate and effective renal plasma flow are also decreased. Serum creatinine and serum cystatin-C levels increase by 10-20% and return to normal following LT4 therapy (38). Total body sodium is essentially increased in hypothyroidism. The excess sodium is thought to bind to extracellular mucopolysaccharides. Reduced free water clearance is seen in hypothyroidism. Some studies have shown elevated levels of serum vasopressin (AVP). Inappropriate release of AVP in some hypothyroid patients may result in a predisposition to low sodium levels by dilution (39).

Increased serum uric acid levels have been shown in men and postmenopausal women with hypothyroidism due to the reduced renal blood flow (40). Some patients may experience mild hypocalcemia. Total magnesium levels may be increased; however, the bound fraction and urinary excretion are decreased with no change in serum potassium levels (41).

In conclusion, renal blood flow and glomerular filtration rate are decreased in hypothyroidism, renal urine dilution capacity is reduced, and hyponatremia may occur in cases with deep hypothyroidism and elevated serum creatinine levels (42).

The effect of hypothyroidism on cardiovascular system

Thermogenesis at tissue level is decreased by 5-8% in hypothyroidism. Peripheral arteriolar resistance is increased by the direct effect of T3 in vascular smooth muscle cells. The final cardiac load and diastolic blood pressure are also increased. Decreased myocardial contractility, cardiac chronotropy and inotropy are observed, resulting in a cardiac output drop to under 4.5 L/min (43). Achieving euthyrodism

normalizes peripheral vascular resistance and diastolic blood pressure (44).

Blood supply is reduced in both myocardial and peripheral tissues due to decreased cardiac output. The reason underlying the lack of ischemic symptoms despite reduced blood supply to myocardium is the simultaneous reduction in myocardial oxygen consumption. Cardiac contractility tends to decrease in hypothyroidism due to the myxedematous changes in myocardial fibers. The compensatory elongation of myocardial muscle fibers in order to perform the existing functions results in cardiomegaly in both right and left heart chambers. Post-treatment improvement appears to be slow and progressive within 3 weeks to 10 months. Decreased interstitial fluid also contributes to the improvement (43, 44).

Pericardial effusion is another factor responsible for the cardiomegaly seen in hypothyroidism; however, it is often mild and does not vastly affect cardiac hemodynamic. In addition to pericardial effusion, pleural and peritoneal effusions may also occur in hypothyroidism (45).

The effect of hypothyroidism on atherosclerosis

Atherosclerosis is reported to increase in hypothyroidism through several pathogenetic pathways (46). Total cholesterol and particularly LDL-C are increased with hypothyroidism. Increased plasma homocysteine levels which return to normal values after treatment have been shown in hypothyroid patients (47). Reduced non-HDL cholesterol levels have been observed following hormone replacement therapy both in subclinical and pronounced hypothyroidism (48). A population study conducted in the Netherlands has shown that subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction (49). Increased epicardial adipose tissue (EAT) has also been associated with atherosclerosis and increased EAT has been shown both in subclinical and overt hypothyroidism cases compared to healthy euthyroid controls (50). The increased EAT in hypothyroid patients has been demonstrated to regress after treatment and this is suggested to be a contributing factor to the atherosclerotic process seen in hypothyroidism (15).

Conclusion

In hypothyroidism, BMR is thought to decrease owing to the effect on hypothalamic nuclei via the central route and the reduced thermogenic effect on peripheral tissues. Body weight is increased in hypothyroidism and then decreased after treatment; however, the current literature is conflicting on whether hypothyroidism actually leads to obesity (increased adipose tissue). Atherosclerosis increases in hypothyroidism and in light of the currently available literature, the factors responsible for this increase may include elevated LDL-C, increased homocysteine levels, diastolic hypertension, predisposition to hypercoagulability as well as the increased insulin resistance and EAT as reported in some studies. However, there may be other pathogenetic pathways which would clarify the effect of hypothyroidism on atherosclerosis and further studies are therefore required in this field.

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The state and importance of motorcycle injuries in progression with trauma etiology

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Abstract

Objective: Motorcycle injuries have shown a progression in last years in trauma patients admitted to our clinic. The aim of this study is to evaluate statistically whether the motorcycle accidents incidence is really has a progression or not.

Method: The study involved 180 patients (87 women, 93 men) operated for the fractures after a motorcycle crash between the first six months of 2002 and 2007. The injury patterns have been investigated if there was a significant increase or not. The mean age was 45.2 years (min. 1year-max. 87 years). In Group I; 50 patients (22 women, 28 men) were included which operated in the first 6 months of 2002. The mean age was 44.8 years (min.1 year-max. 85 years). In Group II; 130 patients (65 women, 65 men) were included which operated in the first 6 months of 2007. The mean age was 45.7 (min. 3 years-max. 87 years).

Results: We compared two groups and found a significant 3.425 increase in motorcycle injuries contrary to 0.075 decreases in falls, 0.023 decrease in traffic accidents within the vehicle, 0.013 decreases in traffic accidents out of the vehicle, 0.616 decreases in sports injuries, 0.25 decreases in gunshot injuries. This increase in motorcycle injuries is statistically significant.

Conclusion: We have found significant increase in motorcycle injuries statistically. The importance of this, it affects younger population, and they bring out high morbidity. Since; we think that motorcycle injuries must be stated especially in literatures. We must warn our colleagues to state these injuries, and must take precautions against this problem.

Key Words: trauma etiology; motorcycle injury

Introduction

Major causes of trauma lead to fractures in the human body are; falls, traffic accidents, shotgun wounds, and sports injuries. Distribution of these etiologies may vary according to the age group, geographic conditions, socio economic status of the population. As the years pass, these etiologies may show an increase or decrease. In addition, new causes will show up due to the developing technologies. While low-energy traumas like simple falls affect the older population, high-energy traumas like falls from height affect the younger population.

Lower socio economic population in low-income and middle-income countries (pedestrians, motorcyclists, passengers in buses and trucks) are under higher risk of morbidity, and mortality due to the traffic injuries because of their capacity of purchase (use mass transportation generally). Furthermore, these populations take limited first aid during the injury (1).

Although generally stated as accidents, it is actually intended to say as road traffic injuries (2). This concept includes; accidents within the car and out of the car. The traffic injuries occur out of the car means that the crashes with the pedestrians, cyclists, and motorcyclists. A serious increase in one of these injuries needs to be reviewed individually out of the general conception.

Motorcycle riding, in general, has a reputation for being dangerous (3). Even though people drive any vehicle, faces with injury or death risks, there are remarkable differences in terms of death rates in different driving categories. Especially pedestrians-which are easily injured- and two wheelers are under higher risk compared to the ones within the car and also they take the major interest (2).

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The motorcycle riders and passengers had a casualty rate nearly fifteen times that of car occupants and they account for 15% of those are killed or seriously injured (4).

Motorcycle injuries involve multiple anatomical areas including head, abdomen, and thorax, and show a preponderance of musculoskeletal injuries in the form of fractures and dislocations (3, 5-7). Fractures are usually open, contaminated, and markedly comminuted (3, 5). A mortality rate of 3–6% has been reported (3, 4, 7). Up to 20% of patients required treatment in an intensive care unit (3). An average of 170 motorcycle crash victims required hospital admission per year in the Yorkshire region alone (4). However, there is no data concerning motorcycle injuries in our country, it is indicated that %17,8 of the patients admitted to emergencies for trauma (9). Alcohol use has been implicated in up to 70% of all fatal and non-fatal motorcycle road crashes (3). It has been shown that the risk of fatal injuries in motorcycle crashes are related to the engine capacity of the motorcycle, the size of the vehicle collided against and the direction of collision (4).

The relative risk of being killed or seriously injured (KSI) has been found higher in male and older drivers, greater motorcycle engine size and motorcycle speed, early morning, at the weekends, in the spring and summer, under fine weather, in darkness without street lights, collisions between bus/coach, at uncontrolled junctions (8).

An increase in motorcycle injuries has been observed in trauma cases admitted to our clinic in recent years. Is there really an increase in motorcycle injuries recently, confirming our clinical observation? The purpose of this study is to evaluate statistically the motorcycle injuries incident really increasing or not and also to draw attention of our colleagues and of the society.

Material and Methods

For this purpose, the injury patterns of the patient population which operated for fractures by the Ege University Orthopaedics & Traumatology Trauma Group as a result of trauma in first six months of 2002 and in first six months of 2007 are stated, and it is statistically investigated whether there is a significant increase or decrease in trauma etiologies (falls, accidents within the vehicle, accidents out of the vehicle, motorcycle injuries, sports injury, and shotgun injuries) past five years period. Trauma etiologies have been obtained from the patients clinical records. The reason we select the patients only operated in our clinic between these periods was the requirement for obtaining the number and etiological data of the patients more accurate. It is not possible to obtain the real number and etiology of the patients which admitted to emergency service, especially the outpatients. Therefore, the patients we obtain accurate data about them, are considered in this study.

One hundred and eighty patients are included in this study. There were 93 male and 87 female, with a mean age of 45.2 years (min. 1 year–max. 87 years). Group I consisted of 50 patients operated in first six months of 2002, 22 female, 28 male, with a mean age of 44.8 years (min. 1 year-max. 85 years) and Group II consisted of 130 patients operated in first six months of 2007, 65 female, 65 male, with a mean age of 45.7 years (range, min. 3 years-max. 87 years). We studied whether there is a significant change or not in trauma causes of the two groups in the same period of both 2002 and 2007 statistically. Vehicle injuries are analyzed separately as injuries within the car and out of the car in our study. The “vehicle” was ment here is non-motorcycle (bus, truck, etc.) vehicles.

Statistical Analyses: In statistical analyses, Chi-square Test and Ficher Exact Test were utilized. The alfa value was taken as 0.05 in this statistical analysis.

Etiologic distribution and arrangement was: In group I; fall 32 patients (64%), injury within the vehicle 8 patients (16%), injury out of the vehicle 4 patients (8%), sports injury 3 patients (6%), motorcycle injury 2 patients (4%), and shotgun injury 1 patient (2%). In group II; fall 77 patients (59.2%), motorcycle injury 23 patients (17.7%), injury within the vehicle 16 patients (12.3%), injury out of the vehicle 9 patients (6.9%), sports injury 3 patients (2.3%), and shotgun injury 2 patients (1.5%) (Figure 1).

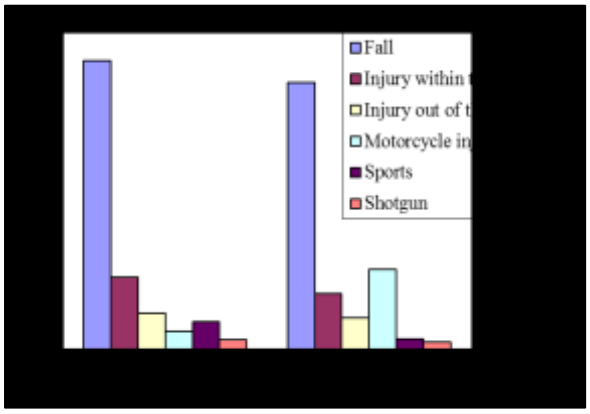

Figure 1: Distribution of trauma etiologies according to the percentages

While motorcycle injury takes the fifth place between trauma etiologies in 2002, it went as high as second place in 2007. When the two groups have been compared; It is established as a 0.075 decrease in falls, 0.023 decrease in injuries within the car, a 0.013 decrease in injuries out of the car, a 0.616 decrease in sports injuries, and a 0.25 decrease in shotgun injuries, compared to an 3.425 times increase in motorcycle injuries.

Table 1: Numerical and proportional distribution of trauma etiologies of the whole study group (180 patients) according to different age groups and different trauma etiologies

	<15	15-45	>45	Total
Falls	13 %11.93 %68.42	16 %14.68 %27.59	80 %73.39 %77.67	109 %100 %60,56
Injuries Within the Vehicle (IWV)	0 %0 %0	16 %66.67 %27.59	8 %33.33 %7.77	24 %100 %13.33
Injuries Out of the Vehicle (IOV)	3 %23.08 %15.79	6 %46.15 %10.34	4 %30.77 %3.88	13 %100 %7.22
Motorcycle Injuries (MI)	1 %4 %5.26	18 %72 %31.03	6 %24 %5.83	25 %100 %13.89
Shotgun Injuries (ShotgunI)	0 %0 %0	1 %33.33 %1.72	2 %66.66 %1.94	3 %100 %1.67
Sports Injuries (SportI)	2 %33.33 %10.52	1 %16.67 %1.72	3 %50 %2.91	6 %100 %3.33
Total	19 %10.56 %100	58 %32.22 %100	103 %57.22 %100	180 %100 %100

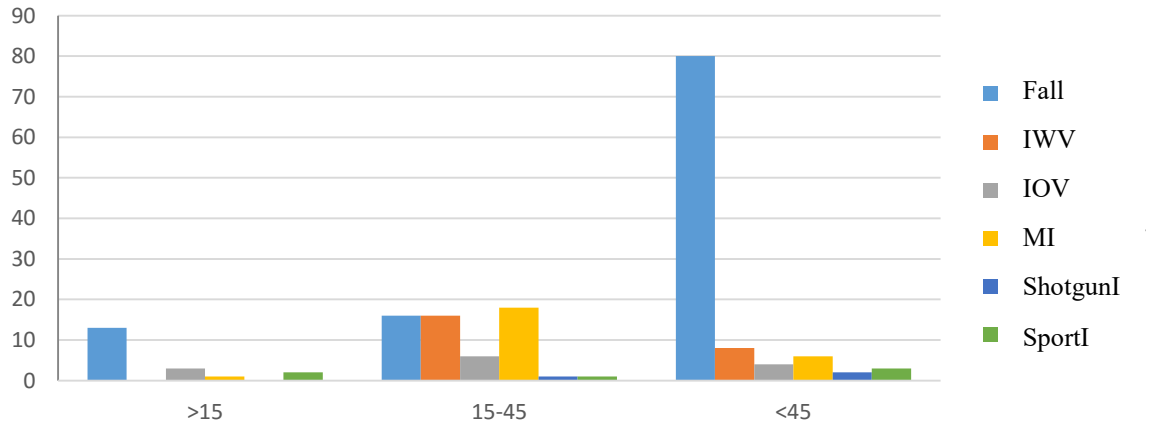

Figure 2: Proportional distribution of trauma etiologies, when investigated according to age groups of total patient population.

These changes in all etiologies except motorcycle injuries have not been found statistically significant (p=0.057, Chi-Square test) while, this increase in motorcycle injuries has been found statistically significant according to Ficher Exact test (p=0.016, power=80%).

To determine the increase in motorcycles between this time periods, we referred to Transport Authority of İzmir. The number of motorcycles in 2002 was 76612, while it was 130216 in 2007. There was a 1.7 increase in the number of motorcycles at that period of time.

In the whole group of 180 patients as seen in figure 2; 109 patients were exposed to fall (60.56%), 24 patients were exposed to injuries within the vehicle (13.33), 13 patients were exposed to injuries out of the car (7.22%), 6 patients were exposed to sports injury (3.33%), 25 patients were exposed to motorcycle injury (13.89%), and 3 patients were exposed to shotgun injuries (1.67%). When this data reviewed according to age groups; from 19 patients under 15 years of age, 13 were exposed to fall (68.42%), 3 were exposed to injury out of the vehicle (15.79%), 2 were exposed to sports injury (10.52%), and 1 was exposed to motorcycle injury (5.26%). There was no injury within the vehicle and no shotgun injury. From 58 patients between 15-45 years of age group, 18 were exposed to motorcycle injury (31.03%), 16 were exposed to fall (27.59%), 16 were exposed to injury within the vehicle (27.59%),

6 were exposed to injury out of the vehicle (10.34%), 1 was exposed to sports injury (1.72%), and 1 was exposed to shotgun injury (1.72%). From 103 patients over 45 years of age; 80 were exposed to fall (77.67%), 8 were exposed to injury within the vehicle (7.77%), 6 were exposed to motorcycle injury (5.83%), 4 were exposed to injury out of the vehicle (3.88%), 3 were exposed to sports injury (2.91%), 2 were exposed to shotgun injury (1.94%) (Table 1, Figure 2).

When we investigated whole study group, totally 25 patients were exposed to motorcycle injury. There was 1 patient under 15 years of age (4%), 18 patients between 15-45 years of age (72%), and 6 patients over 45 years of age (24%) (Table 1). It is stated, motorcycle injuries occur most often in 15-45 years of age group, and it is the first etiological reason with 31.03% in this age group.

Discussion

Traffic injuries are a major but neglected global public health problem. Too often, road safety is treated as a transportation issue, not a public health issue. Traffic-related injuries are often treated as transportation issues, called 'accidents', although most could be prevented (2). Rendering of scientific data about traffic injuries will provide to come over and to prevent this injuries better.

According to the WHO Report of Road Safety 2005, 1.2 million people are killed every year road traffic crashes around the world. Up to 50 million people are injured, many suffering life-long disability (2). Motorcycle crashes continue to be a major cause of fatal road traffic injuries (4). Among these fatal head injuries, bicyclists and motorcyclists represented over 55% of all victims (2). It is stated as injuries to the head, neck and chest were responsible for most severe injuries. Thoracic and abdominal trauma as well as pelvic ring fractures associated with long bone injuries appears to be the secondary factors contributing to reduced survival (4). A delay in diagnosis and treatment can influence the final outcome significantly. Long bone fractures were the commonest injury accompanying to motorcycle accidents. It is reported as lower and upper extremity, head and thoracic cage are the most affecting parts of the body in motorcycle injuries and the most important variable affecting mortality in motorcycle crashes is head injury (4).

The study of Ankarath et al. (4) thus important to state this condition of the1239 patients who admitted to various hospitals by motorcycle crash concluded in this study of Ankarath et al., 11.8% had head and facial injuries, 17.4 % had chest trauma, 12.8 had abdominal trauma, 10.4 % had spinal injury, 94.3 had axial skeletal injury, 0.3 had crush injury, 0.2 had peripheral arterial injury. The detailed distribution of skeletal injuries as follows: 13.2% had pelvic injuries, 17% had femoral shaft fractures, 0.3% had femoral neck fractures, 29.8% had tibial fractures, 11% had ankle fractures, 3.7% had forearm fractures, 5.4% had humeral fractures, 7.6% had clavicular fractures, 2% had scapular fractures, 7.4% wrist fractures, and 2.7% had fractures in the hands. 41 of these patients (4.1%) were rear seat passengers. Of the 1239 patients requiring hospital admission, 74 died (6%). The lower thoracic and upper lumbar area of the spine was the most common site of involvement. Thoracic spine fractures are more likely to be associated with neurological damage, but mortality is more highly associated with cervical spine involvement (4).

Correspondingly, in a prospective analysis of the injuries of off-road competition motorcyclists (3), it is reported as 10% received injuries that required attention from a medical response unit, the majority (85%) of those injuries sustained a mild injury when the Injury Severity Score (ISS) is to be considered, 54% of those injured were first year rookies, speeds were below 50 km/h in the majority of accidents (80%), the most frequently injured anatomical regions were the extremities (57%), the most common types of injury were ligamentous (50%), and the most common fractures were those of the foot and ankle (36%). Speeds and experience were not statistically correlated with severity. In the street riders, ISS are found to be higher significantly than the off-road competition motorcyclists (3, 7).

In our study, the patient population consisted of patients operated for the fracture who survived after trauma. Therefore, these numbers consist of patients who had fractures that need operation, not whole admissions to hospitals caused by the etiological factors of trauma. In our opinion, this is the appropriate group for this purpose. If we investigate the etiological factors, fall seems to be the major cause of the fractures in both groups. We think in older population these fractures occur mostly due to simple falls in osteoporosis background. The road accidents, except motorcycle injuries, are discussed separately in our study group as accidents within and out of the vehicle. Thus these ratios are low. When the two groups reviewed together the road accidents were 24% in 2002, and were 19.2% in 2007. Sports injuries are sited in lower grades in both time periods. One of the important factors for this issue is our study group which consist only fractured and operated patients. Simple ligamentous injuries and ligamentous injuries that required operation have not been considered in our study groups. When two groups compared, 0.075% decrease in falls, 0.023% decreases in injuries within the car, 0. 013% decrease in injuries out of the car, 0.616% decrease in sports injuries, 0.25% decrease in shotgun injuries is reported. While in 2002 motorcycle injuries were in fifth place with 4% percentage, it took second place in 2007 with 17.7%.

Those changes in all etiological factors except motorcycle injuries, is found not statistically significant (Chi-square Test, p=0.057). However, those increase in motorcycle injuries is found statistically significant (Ficher Exact Test, p=0.016 power=80%). The major cause of this increase seems to be the growing number of riding motorcycles due to multiple reasons. Between these periods, there is a 1.7 times increase in registered motorcycle number according to Transport Authority of İzmir database.

The empirical results presented show the important contribution of economic development to mobility, which leads to increased motorization and increased exposure to risk (2). Parallel to this increase, the infrastructure and the security of the roads must be redesigned. Technical and mechanical training of the motorcycle riders must be developed and supervised.

The authors conclude that measures to prevent injury are more important than improved treatment (4). As follows, the significant difference in the GCS between the patients wearing helmets and the un-helmeted group supports the continued use of a protective headgear (4).Therefore, we think it is necessary to wear helmets, shoulder pads, chest protectors, gloves, hip and knee pads, under roost protectors, and hip-knee pad supported boots. Li et al. reported the major morbidity in road traffic injuries affected the 15 – 44 year age group. Also they reported, the morbidity of children up to the age of 15 years represented 3.40%, morbidity in the 15 – 44 year age group was 64.86%; it was 70.46, in the 45–65 year age group, which accounted for 25.65% (2).

We reviewed our study group according to the age intervals to reveal the importance of the trauma causes (Figure 2-3). Accordingly, fall is stated in first place with a 68.42% under 15 years of age group, while injuries out of the vehicle took the second place with 15.79%, and sports injury was third with 10.52%. This age group is tended to be the most dense time period of falls and injuries either caused by both playing and sports. In addition, it is a more likely situation that the children to interpose road traffic injuries as pedestrians. When over 45 years of age group has been investigated, falls take first place with a77.67%, while injuries within the vehicle is at second place with a 7.77%, and motorcycle injuries is the third with a 5.83%. As the fractures due to simple falls based on osteoporosis becomes prevalent over 55 years of age, consists of this age group, it is rendered falls the major cause in this group. In 15–45 years of age group, the motorcycle injuries are at first place with a 31.03%, while falls and injuries within the vehicle at second place with 27.59%, and injuries out of the vehicle in the third place with 10.34%. This age interval involves the most frequent use of motorcycles, thus it is critically important that states motorcycle injuries role in trauma etiologies. And the overall rates are substantially high. In addition, the intensity of situation manifests was clearer. The motorcycle injuries stand at first place in trauma etiologies, owing to the fact that we split the road traffic injuries as injuries within the vehicle and injuries out of the vehicle. If these injuries have reviewed together; the road traffic injuries have been at the first place and motorcycle injuries at the second in trauma etiologies. But it is more important that motorcycle injuries solely, have considerably approximate to road traffic injuries in this age group and in its present form, it is so wide, that it could not be considered in road traffic injuries. Therefore it supports our theory that motorcycle injuries must be reviewed separately from the road traffic injuries. Additionally, when the patient groups subjected to motorcycle injuries have been reviewed in figure 2, it has been stated that 4% of these are under 15 years of age, 72% are between 15-45 years of age, and 24% are over 45 years of age. Although, the most prevalent period of motorcycle injuries seems to be between 15-45 years of age, it is the first etiological factor of this age group with 31.03%.

The weak side of our study is the limited number of patient population because of our emergency clinic does not have an appropriate and attainable database of referred patients. However, this study captures the population's numerical and periodical section in a real and true manner, and puts an emphasis on importance and results of this increase.

Conclusion

As a result, it is noteworthy that, motorcycle injuries show a statistically significant increase, affect the younger patient population, and mostly cause poly-traumatic injuries. Therefore, we think that, while trauma etiologies are counted, motorcycle injuries must be reported separately from the road traffic injuries in the studies. In recent years, motorcycle injuries have been added to the etiological factors of traumatic injuries and became a more serious problem in our country. In view of this problem, necessary precautions and attention of our society must be taken.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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Effects of aminoguanidine treatment on endothelial nitric oxide synthase expression and nitric oxide levels in streptozotocin induced diabetic rats

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Abstract

Objective: Formation of advanced glycation end products (AGE) in Diabetes Mellitus contribute to endothelial dysfunction by permanent modifications of proteins and decrease NO concentration which regulate vascular tonicity and thus endothelial functions. We investigated the effects of AGE inhibitor aminoguanidine (AG) treatment on endothelial nitric oxide synthase (eNOS) expression and NO levels in Streptozotocin induced diabetic rats.

Material and methods: 38 male Sprague-Dawley rats were separated into 4 groups. Group 1 (n=9) was control group without any intervention (C group). Group 2 (n=10) received AG in drinking water (C+AG group). Third (n=10) and fourth (n=9) groups received 65 mg/kg Streptozotocin intraperitoneally to induce diabetes. Group 3 was followed without further intervention (DM group). Group 4 received aminoguanidine in drinking water (DM+AG group). After 12 weeks, serum NO levels were determined with chemiluminescence and eNOS expressions in heart and kidney tissues were determined with Western-Blot together with blood glucose and HbA1c levels.

Results: Serum NO levels were significantly lower in DM ($P<0.001$) and C+AG ($P<0.0005$) groups compared to C group. There was no significant difference between the NO levels of DM and DM+AG groups. eNOS protein levels in heart tissues were significantly lower in DM group ($P<0.05$) than the C group. eNOS levels were significantly higher in DM+AG ($P<0.01$) than DM group. There was no significant difference in eNOS levels in kidney tissues among the groups. The results were compared with Mann-Whitney U test.

Conclusion: Decreased NO levels in DM group were consistent with the literature. eNOS expression in heart tissues were decreased in DM group, their concentration were increased with AG therapy. Further studies are needed to elaborate the effects of AG in tissues and the side effects observed in some studies.

Key words: Diabetes Mellitus, Streptozotocin, Aminoguanidine, Nitric Oxide

Introduction

Micro and macrovascular complications are a prominent cause of morbidity and mortality in diabetic patients. Endothelial cells have an important role in the maintenance of vascular tonus, platelet aggregation and secretion of vasoactive substances, and endothelial dysfunction is one of the disorders that can be observed, starting from very early stages in diabetes. Disturbances in nitric oxide (NO) synthesis from L-arginine by the activity of endothelial nitric oxide synthase (eNOS) in endothelial cells have been implied and investigated in the endothelial dysfunction observed in vascular complications of diabetes. Apart from being a very potent vasodilator, NO has anti atherogenic properties by decreasing thrombocyte and leukocyte adhesion to endothelium and inhibiting smooth muscle cell proliferation (1). There are various articles which state that endothelial vasodilatation mediated by NO is increased, decreased or unchanged in insulin dependent diabetes models (2). Also, formation of advanced glycation end products (AGE) has been suggested to be related with endothelial dysfunction in diabetes (3). Aminoguanidine, which inhibits the formation of AGE has been suggested to increase vasodilatation and slow down the formation of diabetic nephropathy (4).

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We aimed to investigate the changes in NO levels and the expression of NOS in heart and kidney tissues in a streptozotocin induced diabetes rat model and examine the effects of aminoguanidine on serum NO levels and the expression of tissue NOS isoenzymes.

Materials and methods

38 ten week old male Sprague-Dawley rats were included, which were divided to 4 groups and were fed with standard diet containing 20 % protein. Group 1 (n=9) was followed as control group without any intervention (C group). Group 2 (n=10) received 1 g/L/day aminoguanidine (ICN Biomedicals Ohio, USA) in drinking water (C+AG group). In order to induce diabetes, third and fourth groups received a 65 mg/kg single dose of streptozotocin (STZ) (Sigma, St. Louis MO, USA) intraperitoneally (5). Rats with a blood glucose level above 200 mg/dl in a blood sample taken a week later from the caudal vein were regarded as diabetic. Group 3 (n=10) were followed without any further intervention (DM group). Group 4 (n=9) received 1 g/L/day aminoguanidine in drinking water (DM+AG group). 12 weeks after the induction of diabetes, the animals were sacrificed by bleeding under ether anesthesia to take intra-cardiac blood and tissue samples from heart and kidneys. Animal experiments were carried in the experimental animal research laboratory of Marmara University School of Medicine. All experiments and handling of animals complied with National Institute of Health Guide for the care and use of Laboratory Animals and were approved by the ethical committee of Marmara University for experimental animals.

Serum glucose levels were determined spectrophotometrically (Modular P800, Roche Diagnostics, Germany) (6). Plasma HbA1c levels were determined using ClinRep Complete Kit (Recipe, Germany) with reverse phase HPLC (Spectra, Thermo Electron Corporation, USA) with UV 1000 Detector at 415 nm (7). Serum NO levels were determined by the detection of photons (based on the principle of conversion of nitrate to NO by vanadium (III) chloride and NO to NO2 after reacting with ozone in a closed environment, and the emission of photons as excited NO2 returns to their ground state) with chemiluminescence with (NO analyser Sievers 280i, USA)(8, 9).

The heart and kidney tissue samples were homogenized (IKA, Ultra Turrax T25, Germany), centrifuged and the supernatant was used to detect the expressed isoforms of NOS (10). Homogenates containing 70 µg protein for heart, and 100 µg for kidney were denatured at 95 ºC in loading buffer (11) and the isoforms were separated with SDS-PAGE (Bio-Rad Protean II xi, USA), together with Rat Brain Extract (Santa Cruz Biotechnology, USA) for positive control and Protein Marker III (Applichem, Germany) as molecular weight marker. The separated isoforms were transferred to nitrocellulose membrane (BioRad Transblot cell, USA) and immunoblotted with antibodies against eNOS and Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) as housekeeping protein (Santa Cruz Biotechnology, USA) (12). Bound antibodies were visualized with amplified horseradish peroxidase bound secondary antibodies (BioRad, USA) and band intensities were digitized (Vilber Lourmat, Germany) in TIFF format and pixel intensities of bands were counted in equal size areas with ImageJ software and expressed as pixel intensity/ug protein (13). The ratios of eNOS protein expression to the expression of housekeeping protein GAPDH were calculated, the ratio of eNOS/GAPDAH of C group was accepted as 1 and the other groups' ratios were calculated and expressed as multiples of 1.

Statistical comparisons of the data were done with non-parametric Mann Whitney U test (GraphPad InStat Version 3.05). The differences between groups were considered significant when $P < 0.05$ with 95 % confidence interval.

Results

The blood glucose level of DM and DM+AG group were significantly increased compared to the C group ($P<0.0001$ and $P<0.01$, respectively). The glucose levels of DM+AG group was also higher than C+AG group's ($P<0.03$).

The HbA1c levels of DM ($P<0.0001$) and DM+AG groups ($P<0.001$) were statistically higher than the C group. There was no significant difference between DM and DM+AG groups.

The NO levels of DM and DM+AG groups were significantly decreased compared to C group ($P<0.001$, and $P<0.0005$, respectively). There was no difference between the NO levels of DM and DM+AG groups, however, C+AG group also had significantly decreased NO levels compared to C group ($P<0.0005$). The results of glucose, HbA1c and NO levels are presented in Table 1.

In the heart tissue, the expression of eNOS was significantly decreased in DM group compared to C ($P<0.05$) and DM+AG ($P<0.01$). The eNOS expressions of C, C+AG, and DM+AG groups were not different. When the expression of eNOS was compared in kidney tissue, there was no difference among groups (Table 2).

The eNOS/GAPDH pixel intensity ratio was significantly decreased in the heart tissues of DM group, when compared to C and DM+AG ($P<0.005$ and $P<0.01$, respectively). C, C+AG, and DM+AG groups were not different. When the eNOS/GAPDH pixel intensity ratio was compared in kidney tissue, there was no difference among groups.

Table 1: Glucose, HbA1c and NO levels of groups presented as median (minimum – maximum)

	C	C+AG	DM	DM+AG
Glucose; mg/dL	174 (162-185)	155$^{\#}$ (142-174)	533* (189-572)	597** (310-751)
HbA1c; (%)	1.09 (0.71-1.50)	1.00$^{\#\#}$ (0.52-1.69)	2.55* (1.54-3.94)	2.01*** (1.13-2.85)
NO; µM	50.5 (38.5-54.1)	37.0**** (36.0-37.7)	34.5*** (28.0-49.5)	30.8**** (18.5-40.5)

*P<0.0001 compared to C, **P<0.01 compared to C, ***P<0.001 compared to C, ****P<0.0005 compared to C, $^{\#}$P<0.03 compared to DM+AG, $^{\#\#}$P<0.0001 compared to DM+AG,

Table 2: eNOS protein pixel intensities/µg protein and eNOS/GAPDH ratios in heart and kidney tissues presented as median (minimum – maximum)

	C	C+AG	DM	DM+AG
eNOS protein pixel intensities in heart tissue (pixel/µg protein)	1.11 (0.88-1.56)	1.015 (0.86-1.50)	0.87* (0.73-1.30)	1.24$^{\#}$ (0.80-1.72)
eNOS/GAPDH ratio in heart	1	1.14 (0.78-1.30)	0.66** (0.53-1.20)	1.01$^{\#}$ (0.63-1.67)
eNOS protein pixel intensities in kidney tissue (pixel/µg protein)	0.78 (0.63-1.05)	0.77 (0.53-0.94)	0.81 (0.66-0.99)	0.85 (0.73-1.11)
eNOS/GAPDH ratio in kidneys	1	1.13 (0.65-2.00)	0.98 (0.76-1.58)	1.08 (0.87-1.18)

* P<0.05 compared to C, ** P<0.005 compared to C, $^{\#}$ P<0.01compared to DM.

The eNOS expressions in heart and kidney tissues visualized with western blot are shown in Figure 1.

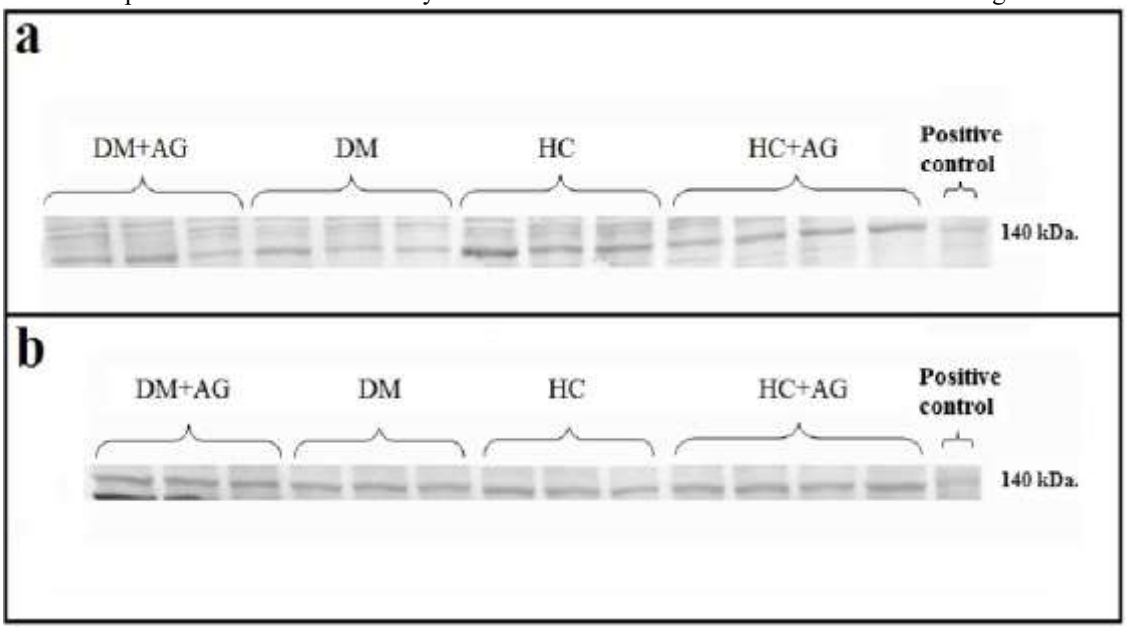

Figure 1: The representative western blots of (a) heart and (b) kidney tissue eNOS expression

Discussion

Endothelial dysfunction is closely related with the micro and macrovascular complications of diabetes (14). Increased formation of AGE as a result of hyperglycaemia has been suggested as one of the mechanisms contributing to endothelial dysfunction (3). Advanced glycation is a relatively long process, taking weeks to form, and affect structural proteins with a long half-life (15). Therefore, in this study we chose to wait 12 weeks after the induction of diabetes before taking the samples to be analysed. It has been shown that inhibition of advanced glycation can decrease the rate of complications such as diabetic nephropathy, retinopathy and neuropathy (16). Aminoguanidine is a nucleophilic hydrazine molecule which was attempted to be used an anti-glycation agent.

We aimed to form a model of diabetes in rats with streptozotocin and after waiting for 12 weeks for the formation of AGE, we wanted to investigate how serum NO levels and tissue eNOS expression changes in this model and see if the effects of aminoguanidine are related to serum NO levels and eNOS expression.

The significant increase in glucose and HbA1c levels in DM and DM+AG groups showed us that the induction of diabetes model was successful. HbA1c is the glycated form of haemoglobin and precedes AGE formation. Aminoguanidine interacts with dicarbonyl compounds derived from glucose to form 3-amino-1,2,4-triazin molecules and thereby inhibit AGE formation. It does not have any effect on HbA1c but it has been suggested to compete with glucose for protein glycation in a dose dependent manner (17). Our finding that HbA1c was relatively less increased in DM+AG group was compatible with this suggested. The fact that there was no difference in C and C+AG groups HbA1c levels could be resulting from the fact that AGE formation was not increased in either groups or HbA1c not being elevated enough to cause any difference.

The NO levels were significantly decreased in DM and DM+AG groups compared to C group, but were not different from each other. Also, C+AG group had significantly lower NO levels compared to C group. Apart from other free radical species, NO has physiological functions in low concentrations. Smooth muscle relaxation, inhibition of platelet aggregation, anti-inflammatory and antioxidant effects and effects on kidneys and immune system are among the suggested functions. At the same time, some harmful properties such as consumption of antioxidants, inhibition of some enzymes, DNA damage and lipid peroxidation have also been attributed to NO. The differences in the various reports regarding the status of NO in insulin dependent diabetes models can be attributed to the duration and severity of diabetes, choice of tissue and vasodilator agent investigated. The decrease we observed in DM and DM+AG groups is in compliance with the reports that state NO mediated vasodilatation is impaired in diabetes (18-20). The absence of any difference between DM and DM+AG groups suggest that aminoguanidine does not show its effects through NO related mechanisms. Although not significant, the tendency to decrease in DM+AG and C+AG groups with respect to DM and C groups could also result from aminoguanidine having NOS inhibiting properties (17).

As in atherosclerosis, there are various and sometimes contradicting results about the expression and activity of eNOS in diabetic animal models. There are reports which state that the expression of eNOS from human aortic endothelial cells is decreased (21) or increased (22) under hyperglycaemia. Human glomerular endothelial cells exhibit increased expression of eNOS and decreased formation of NO under hyperglycaemic conditions (23). There are also other studies which report increased eNOS mRNA and protein (24)and contradictory decreased cGMP formation (25) in diabetic animals. Although research parameters such as the duration and type of diabetes, the tissue analyzed and the molecule investigated may vary, it is generally accepted that a change occur in NO related biological processes with the formation of diabetes (2). Our finding that the expression of eNOS was decreased in DM group in heart tissue was parallel to Srnivasan's findings which showed that long term exposure to high glucose concentrations decreased eNOS expression in endothelial cells (21). Another suggested mechanism is that an increase in transcription factors such as NF-□B due to increased AGE (26) or AP-1 and reactive oxygen species due to hyperglycemia (21) inhibits the expression of eNOS. The observation that the same decrease was not observed in DM+AG group complies with the idea that aminoguanidine had succesfully inhibited the formation of AGE in this group. Aminoguanidine had no further effect on C group, probably because they already did not have an increased AGE production.

However, the observed effects in the heart tissue were not present in kidneys and no difference in eNOS expression was observed among groups. This might result both from the formation and effects of AGE may show variations among tissues and the different location and regulation of eNOS among different tissues.

Conclusion

Although we observed that eNOS expression was affected by aminoguanidine, clinical studies regarding the use of this drug in the prevention of diabetic complications were halted in the meantime due to potentially harmful side effects. More studies are required to understand aminoguanidine mechanism of action and characterization of its side effects.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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Transperitoneal laparoscopic treatment of ureteropelvic obstruction:our initial experience: Laparoscopic Pyeloplasty

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Abstract

Objective: Higher morbidity rates, extensive scar tissue formation and longer hospitalization periods of the standard open surgical methods for ureteropelvic obstruction has led to acceleration of minimal invasive techniques. Success rate and clinical outcomes of laparoscopic pyeloplasty has become comparable with open surgery.

Purpose: The aim was to evaluate the clinical results and complications of transperitoneal laparoscopic pyeloplasty in ureteropelvic obstruction.

Material and Methods: Thirty-three patients with ureteropelvic obstruction were enrolled into this study. Eighteen patients underwent Anderson-Hynes dismembered Pyeloplasty and 15 underwent Y-V plasty. Patients were followed-up at postoperative 3., 6. months and then yearly. Partial or total relief of symptoms and improvement in diuretic renogram were accepted as success.

Results: Median age was 34.5±15.5(13-74) years, number of males were 13 (39.4%) and females were 20 (60.6%). Median Body Mass Index (BMI) was 25.3±15.4(18.5-33.4). Eight were asymptomatic, and 23 had intermittent pain, preoperatively. Fourteen cases had left ureteropelvic obstruction (42.4%) and 19 had in the right kidney. Intraoperatively 19 cases had aberrant vessel. Mean surgery time was 127.9±38.9 (68-245) minutes, median anastomosis time was 20.8±7.3 (8-39) minutes. Median blood loss was 57.1±28.3 (20-150) ml, median postoperative drainage time was 2.6±1.1 (2-7) days. Only one had prolonged ileus and peritoneal irritation findings. Median narcotic and nonnarcotic requirements were 21.5±4.8 (15-30) and 132.6±37.2 (75-200) mg/day, respectively. Median follow-up period was 35.1±13.6 (11-59) months.

Conclusions: Laparoscopic pyeloplasty, is minimally invasive and reliable technique replaces open pyeloplasty in many institutions. Shorter hospitalization, lower postoperative morbidity rates, better cosmetic results and higher success rates can be easily achieved..

Keywords: Hydronephrosis, Ureteropelvic junction, Pyeloplasty, Laparoscopy

Introduction

Ureteropelvic (UP) obstruction is the most common congenital or acquired disease of the upper urinary system that can be seen as a secondary functional impairment or anatomic anomaly (1,2). The most common cause of anatomic defects is the compression of an aberrant artery that supplies the lower pole of the kidney. Other less frequent intrinsic causes are the deterioration of the circular arrangement of fibres and the deposition of intracellular and intercellular non-resilient collagen (3). The most common complaint is flank pain. Major complications are urinary tract infections, renal function loss with a gradual increase and hypertension, although hypertension is rare. Standard open surgical methods that have been applied in UP obstruction treatment result in higher morbidity rates and longer hospitalization periods and they leave extensive scar tissue. Due to these facts, these methods have been replaced by minimally invasive procedures such as laparoscopic or robotic surgery that result in lower morbidity rates and shorter hospitalization periods. In this study, we aimed to retrospectively present the results of 33 laparoscopic pyeloplasties that were performed by two surgeons.

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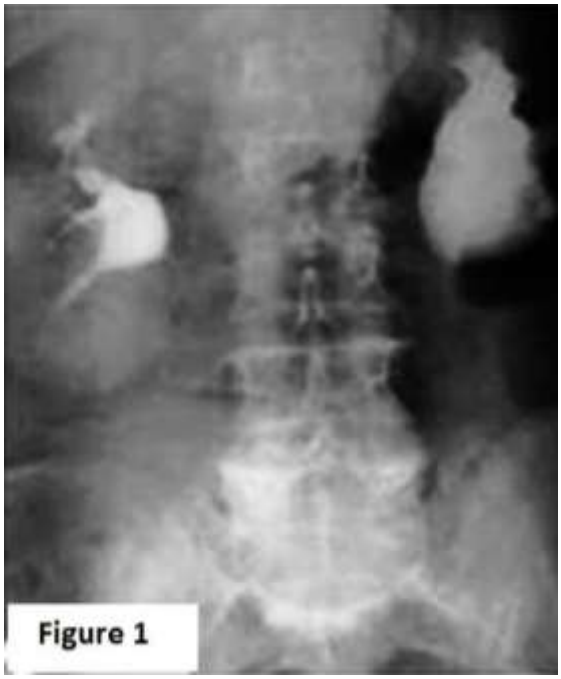

Figure 1: Left hydronephrosis due to ureteropelvic junction obstruction

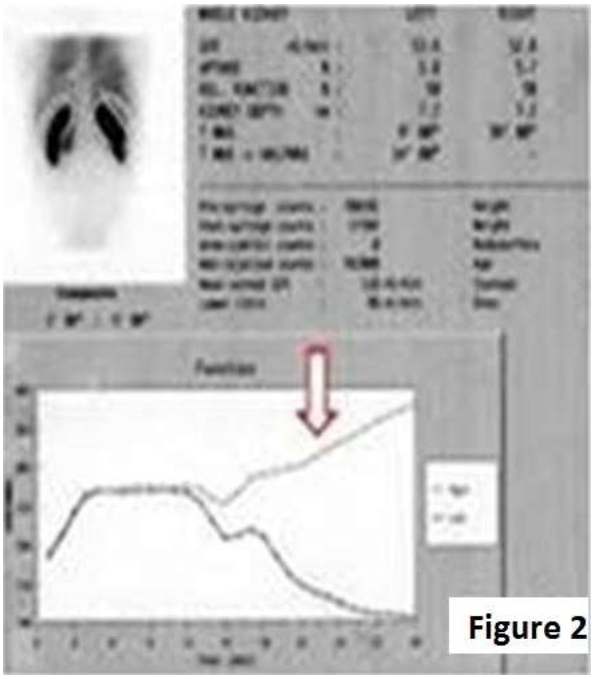

Figure 2: Renal scintigraphy shows radionuclide accumulation on affected side

Material and Methods

Laparoscopic trans-peritoneal pyeloplasty procedures were performed on 33 patients (20 female, 13 male) that had been previously diagnosed with UP stenosis following ultrasound, intravenous urethrography, and diuretic scintigraphy. This study was performed after the Scientific Research Review Board approval was given (23.11.2015/33/30). Written informed consent was obtained from participants or, their parents. All cases were admitted to the institution with flank pain complaint from April 2011 to September 2014. Preoperative demographic data, intraoperative features and postoperative findings were recorded. Complications were evaluated using the Clavien classification system. Cases with hydronephrosis that was revealed by preoperative ultrasound/intravenous urography and that had a $T_{1/2}$ radionuclide excretion time longer than 20 minutes on a renogram were included to this study (Figures 1 and 2).

Success criteria were considered as a radionuclide excretion time shorter than 20 minutes on a renogram, symptomatic improvement, and improvement in renal functions or at least functi,ons remaining at the preoperative level. Urinary tract infection status was documented with a urine culture before the surgery. A preoperative retrograde stent was placed in each case preoperatively.

A one gr intravenous prophylaxis of cefazolin 1gr intravenous prophylaxis was given to all patients before the operation.

Following induction anaesthesia, a nasogastric tube and a 16 F Foley catheter were put in place for each patient. Next, patients were positioned in a 20° lateral decubitis position. A 10 mm optic trocar was inserted to the 5 cm point of the umbilicus with a modified Hasson's technique through a 15 mm skin incision under direct vision. The creation of pneumoperitoneum was obtained by carbon dioxide insufflation at 3.5 L/min until 12 mm Hg pressure was reached. The second port of 5mm was placed over the anterior axillary line, 1cm below the 12th rib. The third port of 10 mm was applied over the same axis, 5 cm cranial of the iliac crest. Three port entries were carried out for each patient. When a fourth port entry was necessary, a flattened suture needle was applied through the abdominal wall under direct vision for traction (Figure 3). The time from the skin incision for the first trocar until the end of last suture placement at the end of the procedure is defined as operating time. The lateral peritoneum was dissected from the Toldt line, and colon was moved medially. Thus, the renal pelvis was released (Figure. 4).

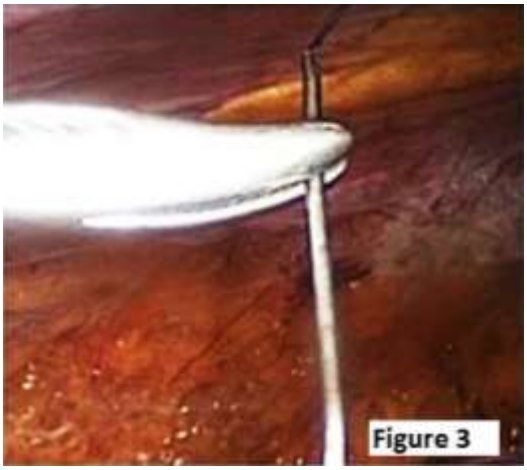

Figure 3: Flattened suture needle was applied through the abdominal wall under direct vision for traction

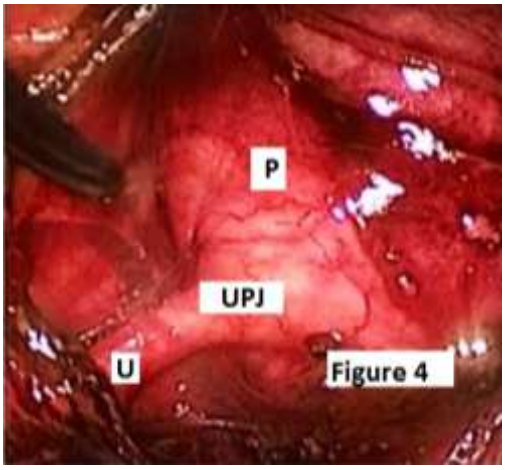

Figure 4: Laparoscopic appearence of ureteropelvic junction obstruction

Table 1: Demographic characteristics, operative and postoperative findings of the patients

Characteristics	Findings
Gender	
Female	20 (60.6%)
Male	13 (39.4%)
Age year±SD (min-max)	34.5±15.5 (13-74)
Laterality (n)	
Right	19 (57.6%)
Left	14 (42.4%)
Pain (n)	
Yes	23 (69.7%)
No	10 (30.3%)
BMI [1] kg/m^2±SD (min-max)	25.3±15.4 (18.5-33.4)
Crossing vessel	
Yes	19 (57.8%)
No	14 (42.2%)
Operation time min±SD (min-max)	127.9 ±38.9 (68-245)
Anastomosis time min±SD (min-max)	20.8±7.3 (8-39)
Blood loss ml±SD (min-max)	57.1±28.3 (20-150)
Complications	
Intraoperative	None
Early postoperative[2]	
Prolonged ileus due to urinary leakage	1 (3%)
Postoperative	
Re-stenosis	1 (3%)
Narcotic analgesic	
Requirement mg±SD (min-max)	21±4.8 (15-30)
Non-narcotic analgesic	
Requirement mg±SD (min-max)	132.6 ± 37.2 (75-200)
Drain retrieval day	2.6±1.1 (2-7)
Follow- up time month±SD (min-max)	35.1±13.6 (11-52)
Length of hospital stay(day±SD (min-max)	2.6±1.05 (2-7)
Success rate	32 (97%)

[1] **BMI:Body Mass Index,** [2] **During hospital stay**

Eighteen cases underwent Anderson-Haynes dismembered pyeloplasty. Y-V plasties were performed on the other 15 cases without aberrant vessels. Renal pelvis reduction was done in two cases. The proximal end of a double J catheter was controlled for its placement in the renal pelvis, the posterior layer of ureteropelvic anastomosis was sutured by 4/0 running vicryl, and anterior face was closed with a second running suture. In one of the cases, a 10 mm kidney stone that was situated in the lower pole of the kidney was laparoscopically removed. Following the completion of anastomosis, the intraperitoneal pressure was decreased to 5 mm Hg and bleeding control was done. Insufflation was terminated after placement of 20 F drain in all cases. Trocar entrance incisions were infiltrated with prilocain and then closed with a No 0 J suture. Pain pump application was routinely done in all cases. The nasogastric tube was drawn away at the end of anaesthesia. All cases were mobilized within a postoperative period of 24 hours.

Results

Evaluation of all cases enrolled into this study revealed that the median age was 34.5±15.5 (13-74) years, and there were 13 male cases (39.4%) and 20 female cases (60.6%). The median body mass index (BMI) was 25.3±15.4 (18.5-33.4). Two of the cases had had abdominal surgery before previously (6%). Eight of the cases were asymptomatic, and 23 had the history of intermittent pain. In one case asymptomatic kidney stone accompanied the UP stenosis (3%). Fourteen cases had UP stenosis in the left kidney (42.4%) while 19 had it in the right kidney (Table 1).

When intraoperative findings were evaluated, an aberrant vessel that supplies the lower pole of the kidney was seen in 19 cases, while in other 14 cases there was no additional pathology that would cause external pressure to the kidney. There was no comorbidity factor in the cases, except for a lower pole kidney stone that was not interfere to the urine flow in one case. The median surgical period was 127.9±38.9 (68-245) minutes, and the median UP anastomosis time was 20.8±7.3 (8-39) minutes. In 32 cases, the operations were performed laparoscopically, however in only one case due to severe peri-pelvisitis the procedure had to be shifted into open surgery. The median blood loss during the operation was 57.1±28.3 (20-150) ml. The median duration of drainage in the postoperative period was 2.6±1.1 (2-7) days. Unfortunately in one case due to urine leakage from UP anastomosis, there was prolonged ileus and peritoneal irritation findings (Clavien grade II). The median need for a narcotic analgesic drug was 21.5±4.8 (15-30) mg/day, and the median need for a non-narcotic analgesic was 132.6±37.2 (75-200) mg/day.

The median hospital stay was 2.6±1.05 (2-7) days, and the median follow-up period was 35.1±13.6 (11-59) months. Double J catheters were removed 4-6 weeks after the operation. At the end of the 3rd month, Patients underwent routine ultrasounds and diuretic renograms and 32 cases were asymptomatic, hydronephrosis was markedly regressed in US, and ureteropelvic obstruction was improved in renal diuretic scintigraphy (Figure 2). In one case only, obstruction continued to the postoperative 6th month..

Discussion

Since the first open pyeloplasty was performed in 1949, this technique has had caught success rate of over 90%. Yet the necessity for an extensive lumbotomy incision, bad cosmetic results, greater risk of higher nerve injury, longer healing and hospitalization periods, and greater analgesic requirements have formed the basis for investigation into less invasive methods, and thus the antegrade endopyelotomy technique has been defined (4). However, the long-term success rate of this technique dropped to 70% in patients with severely deprived renal functions, with a UP stenotic segment longer than 2cm and with the presence of crossing vessel. Moreover, its applicability to selected cases has accelerated the innovations because of its higher success rates. In the early of 1990's laparoscopic pyeloplasty was described (5). As a result of ever advancing technology laparoscopic pyeloplasty has achieved a success rate that is similar to open surgery, and it has been recommended by EAU as a first-line treatment in UP stenosis along with open surgery (6).

Pyeloplasty can be performed with either the transperitoneal or the retroperitoneal approach. Although the transperitoneal approach provides a larger operating area in terms of dissection and suturing, the retroperitoneal approach enables a safer reach to the ureteropelvic area without irritating the peritoneum. Zhu et al. reported a faster reach to the UP area with the retroperitoneal approach, but they reported a shorter anastomosis suturing and shorter total surgery time with the transperitoneal approach (7,8). In this study, despite the increased risk of damage to intraperitoneal organs and prolonged ileus, we preferred the transperitoneal approach since it provided a larger surgical area. (9). We think that since the retroperitoneal approach provides a narrow working area for the surgeon, it should be performed either by more experienced surgeons or at institutions were learning curve has been completed. We experienced intraperitoneal adhesions in two cases due to previous surgeries. However, we performed the procedure laparoscopically with careful placement of trocars and adhesiolysis.

In studies, in which open and robotic laparoscopic pyeloplasty techniques are compared, it can be seen that robotic surgery requires a longer time than the laparoscopic technique. The surgery time in our study is compatible with other study results described the literature (10). The anastomosis time in our study is shorter when compared to retroperitoneal techniques, which is also compatible with findings recorded in the literature (11). Among the factors that shorten the anastomosis suturing period, continuous suturing instead of intermittent suturing, and the preference for the robotic method due to its advantageous three dimensional features instead of the classical method and the completion of a learning curve could need to be mentioned (12). In a meta-analysis in which laparoscopic pyeloplasty and robotic or open pyeloplasty techniques were compared, it has been shown that there was no significant difference between success rates, bleeding risk and complications (10). The need for narcotic or non-narcotic analgesic after in laparoscopic surgery has been found to be lower than for the open pyeloplasty technique (13). In our study, the median need for narcotic analgesics was 21.5±4.8 mg (15-30), which is compatible with what appears in the literature.

Double J-catheter application timing for patients with planned laparoscopic pyeloplasty is a point for discussion. Some authors argue that pre-operative ante grade double J catheter application may not prolong the surgery time (14). Preoperative stent application may complicate pelvic visualization and dissection by decompressing the renal pelvis. We think preoperative cystoscopy and retrograde pyelographies are necessary in order to investigate the presence of other negative factors in the bladder or distal ureter that interrupt indication for pyeloplasty. For this reason, we performed retrograde double J catheterization in all of our cases preoperatively (10).

The most important reason for the formation of UP stenosis is the presence of aberrant vessels. Crossing vessel incidence in the literature was reported to be between 50-70% (15). We observed aberrant vessels in 19 patients (57.6%) in our study. It has been advised that even though aberrant vessels are the most common cause of UP stenosis, other causes should be kept in mind (16). Richstone et al., histologically evaluated tissue specimens of patients with and without vessel compression. They did not demonstrate any pathological finding in 43% of them (17) when there is presence of an aberrant vein, it should be carefully dissected from the artery. If there is a suspicion that the vein might contribute to UP stenosis, it should be obliterated (18). In our study, only one case recurred 6 months after surgery, but 32 patients showed improvement in ultrasonic and renographic findings. Even though the short-term success rate is 97%, limited data in the literature for the long-term success rate may lead us to think that this rate might decrease. However, studies show that failure after laparoscopic pyeloplasty is mostly reported within first two years. Indeed, in our study, the mean follow up time greater than two years revealed no prominent decrease in the success rate (19). The most important factors that determine the success of surgery are the lack of tension in an anastomosis, good drainage, and efficient adhesiolysis. In the literature, it has been stated that the success rate of laparoscopic pyeloplasty is from 92-100% (20). Although some researchers advocate that only objective criteria would suffice, we think that the most important success criterion is symptomatic relief rather than diuretic renography and Whitaker test in follow up controls (21).

Conclusion

At the beginning of the laparoscopy era it was believed that this technique required a long learning curve, but laparoscopic pyeloplasty is now regarded as one of the safest and the most reliable minimally invasive technique used today due to its short hospitalization time, low post-operative morbidity rate, and better cosmetic results. Moreover it has been shown that even if performed by physicians who have only moderate experience, it produces favorable long-term results.

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An extremely rare complication after appendectomy in a child: indicators for omental abscess, CRP and Leukocytosis

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Abstract

A 14 year-old male child underwent appendectomy, and partial omentectomy with the indication of perforated appendicitis. Despite antibiotic therapy at postoperative sixth day, purulent discharge started to ooze from the incision site. Upon detection of a palpable mass in the lower right abdominal quadrant, ultrasonographic examination was performed on the postoperative 14th day which revealed a non-homogeneous hypoechoic mass measuring 50-45 mm with irregular contours. The case was re-operated and a greater omental abscess was found which resected en-bloc. Any evidence of foreign object or residual appendiceal tissue was not found. Postoperative course was uneventful, and the patient was discharged on the 36th postoperative day. Herein, we reported an extremely rare case of omental abscess developed following appendectomy.

Keywords: Appendicitis; Appendectomy; Complications; Omental abscess; Child

Introduction

Development of intraabdominal abscess following appendectomy is an important and potentially fatal complication which requires surgical intervention. Pelvic, subdiaphragmatic, interintestinal, subhepatic, retrocecal, intramesenteric abscesses can develop. Greater omental abscess is an extremely rare condition among intraabdominal abscesses. As reported in previous publications, it can develop on postoperative 16. day (1) or 2 years after the appendectomy (2). Omental abscess is rarely considered in the differential diagnosis of appendectomized patients. This case was reported so as to remind this possibility

Case

A 14-year-old male adolescent was admitted to the Department of Pediatric Surgery of Cengiz Gökcek Obstetrics and Children's Hospital with typical symptoms of appendicitis on November 9, 2015, 96 hours after onset of his complaints . Laboratory parametres were within normal limits, excepting leucocytosis (19.8 (n:4.5-11) 103/µL , and increased CRP 21.6 (n: < 0.6) mg/dl level. Laparatomy for appendectomy was performed through modified Rockey Davis incision. As soon as the peritoneum was opened, abundant purulent discharge was drained from the right iliac fossa, and pelvis. Appendix vermiformis was wrapped with greater omentum. A calcified appendicolith dropped into pelvis from gangrenous, and perforated appendix which was extracted immediately.

Since omentum was hyperemic, and fibrinous, partial omental resection was performed following typical appendectomy. The inflamed area of the omentum was excised and ligated using 3/0 vicryl sutures. A drain was placed in the pelvic cavity, and surgical wound was closed with sutures. Antibacterial treatment was administered (twice daily IV injections of 1 g ceftazidime, and 500 mg metronidazole). The first 5 days body temperature fluctuated between 37.8°C, and 38.2°C from the postoperative 6th day on purulent discharged oozed from the incision site. Despite initiation of antibiotic therapy (trimethoprim/sulfametoxazol and gentamycin) based on antibiotic susceptibility tests, his health state did not improve, and on the following day, (postoperative 14. day) a palpable mass was detected on the right lower abdominal quadrant. An ultrasound (US) examination revealed a non-homo¬geneous hypoechoic mass in the right iliac fossa with irregular contours, and measuring 50 × 45 mm. According to US findings, and typical clinical data, reoperation was planned. Abdominal cavity was opened through the previous incision line, but any purulent collection was not found. Appendectomy loge, and cecum were intact. In the right lower abdominal quadrant greater omentum was palpated as a solid mass Omental mass was excised, and drained purulent material was sent for culture. Greater omentum with dimensions of 4 x 5 cm was peeled away from the terminal ileum without causing any harm (Fig. 1).

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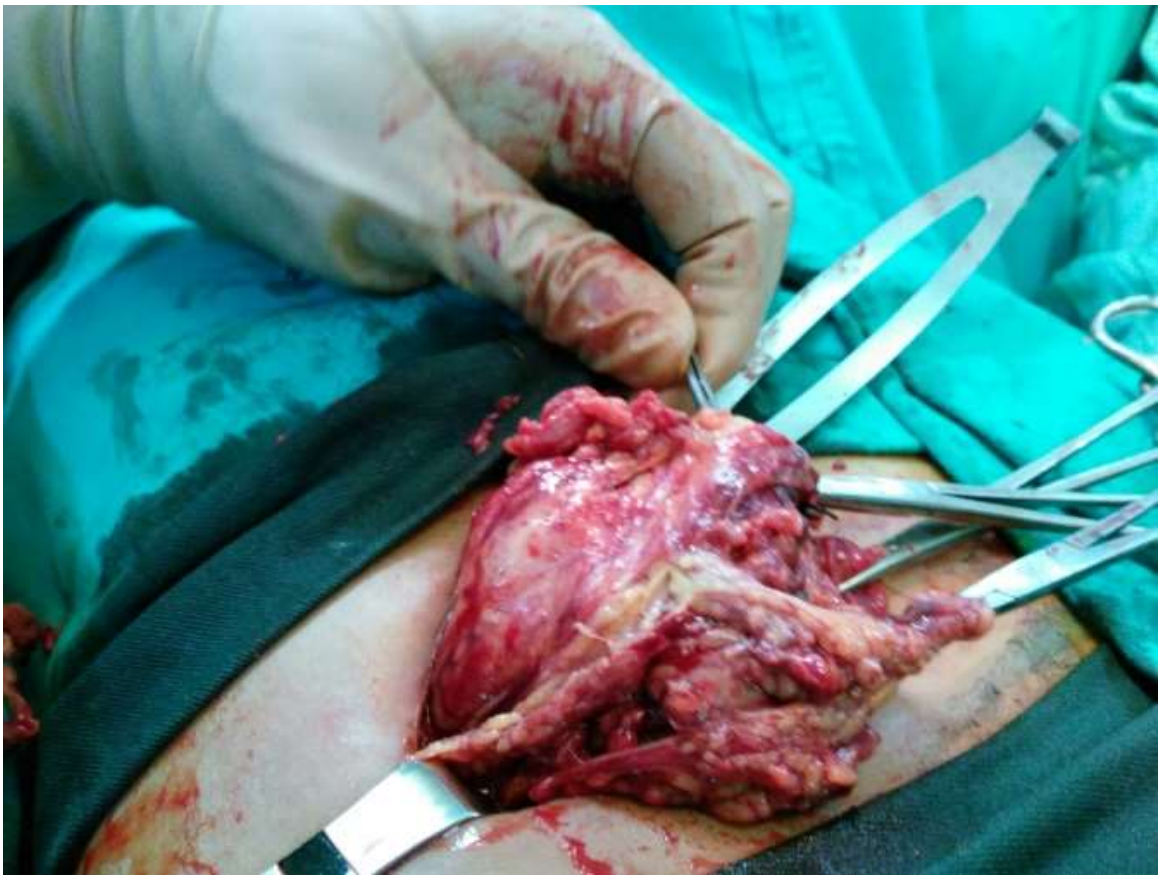

Figure 1: Resected specimen including a part of the greater omentum and the abscess.

Following resection, minimal bleeding was controlled. Based on antibiotic susceptibility test results Escherichia coli sensitive antibiotherapy was initiated. The patient was discharged in a satisfactory condition on the 36th postoperative day.

Discussion

Development of abscess following appendectomy is an extremely rare condition which is nowadays thought to be an unacceptable entity by many surgeons. However articles were published on this issue during 1970s, and 1980s (3,4). Omental abscess is a special version of omentitis, and exists in two types. Primary omentitis develops in patients without history of surgery as a complication of omental torsion, ischemia, thromboembolic lesions, while secondary omentitis evolves as a complication of an inflammatory process in another abdominal organ (4). Omentitis can be classified according to the degree of inflammation. Secondary omentitis is more prevalent than primary omentitis, and solitary forms are more widespread than those associated with abscess. Post-appendectomy purulent omentitis is an extremely rare entity.

The incidence rates of omental abscess have been reported as 0.011% by Cortesi et al, (5), and as 0.02% by Bairov and Golovanov (6). Paliuga reported development of intraabdominal abscesses in three different locations including greater omentum in one of their patients (7).

Almost all patients who developed purulent omentitis during postoperative period of appendectomy have been reported as cases with complicated appendicitis, and destructive (usually gangrenous) appendicitis associated with peritonitis (4,6,8). Most of the cases consisted of patients who had undergone primary appendectomy combined with omentectomy performed because of secondary inflammatory involvement of greater omentum (8). Clinical symptoms of omental abscess include abdominal pain, fever and systemic inflammation. On palpation local tenderness, and most of the time a mass is palpated. This condition does not develop immediately after appendectomy; it can reportedly emerge between 16 days, and 2 years after appendectomy. (1,2). Omental abscess developed long after appendectomy may be mistaken as an intraabdominal tumor (2). Indolent omental inflammation may be provoked in some cases. (1).

For diagnosis, as previously reported in many publications US, CT, and MRI may be used widely in clinical practice. Although some authors have thought that US has a lower diagnostic value in omental abscesses localized close to the abdominal wall (8), we consider US as a valuable diagnostic tool. Electromyography had been used once in the diagnosis of secondary omentitis, however nowadays it an outmoded diagnostic modality. In our case we made the diagnosis of omentitis using only US. In challenging cases, CT may also use locally. (2). Other omental lesions include omental torsion, and infarct (9).

The moıst effective treatment of omental abscess is its removal together with healthy tissue around the well-defined contours of the mass lesion. Drainage of the abscess cavity is another surgical treatment method which should be reserved for special indications which may jeopardize intestinal loops. Laparoscopic drainage may be less invasive in cases with primary omental abscess (10). In our case ileal segments in the omental mass forced us to prefer open surgery rather than laparoscopic approaches in order to prevent intestinal damage. US-guided drainage was not considered due to risk of recurrence of abscess. Since omental abscess developed secondary to infected ligature, drainage of abscess without resection wouldn't be an appropriate approach for our patient. In cases that developed abscess secondary to fecaliths, radical treatment involves opening of abscess, and extraction of the fecalith. Otherwise, possibility of recurrence is very high. (11). Up to now optimal treatment of omental abscess still continues to be omental resection (2,12).

Prevention of purulent omentitis is possible with correct application of omental resection. Omentum should be resected in small parts, and leaving large remnants behind should be avoided (4). The resection line should be extended so as to include non-inflamed, intact tissues (4,6).

Herein, an extremely rare condition with development of greater omental abscess during postoperative period of a patient who underwent appendectomy with the indication of perforated appendicitis was reported. Among intraabdominal abscesses, the possibility of greater omental abscess which has faded into oblivion recently should be always kept in mind as a postoperative complication.

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Peripheral neuropathy as a rare syndrome related to metronidazole usage: Metronidazole may lead to persistent neuropathy

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Abstract

Metronidazole is a potent drug used against some protozoa like Entamoeba histolytica, Giardia lamblia, Trichomonas vaginalis and Balantidium coli, and anaerobic bacteria. It is used for the treatment of alcoholism, Crohn's disease, exophthalmos, rheumatoid arthritis, rosea and acne as well. It is a well-tolerated drug with some kinds of side effects like abdominal pain, headache, nausea and metallic taste. Rarely but severely, pseudomembranous colitis, epileptic seizure, encephalopathy and peripheral neuropathy might be seen. These side effects are generally self-limited. Drug administration should be stopped immediately in case of these side effects' existence. In this article, we presented a case which used metronidazole for hepatic ameobiasis for 18 weeks and developed peripheral neuropathy

Key words: ameobiasis, metronidazole, peripheral neuropathy

Introduction

Metronidazole is a 5-nitroimidazole (Fig 1) compound as potent compound as potent drug used against protozoa (1). It is admitted that metronidazole easily penetrates into cerebrospinal fluid and central nervous system. Neurological symptoms generally occur when it is administered above 2gr. per day (2).

It is also used for the treatment of alcoholism, Crohn's disease, exophthalmos, rheumatoid arthritis, rosea and acne as well. Headache, vertigo, syncope, sleep disturbance, confusion and depression are some of the side effects. Peripheral neuropathy is a rare side effect (3-7). These side effects are generally self-limited but may last for a long time. In this article, we aimed to present a case which used metronidazole for the treatment of hepatic ameobiasis and developed peripheral neuropathy

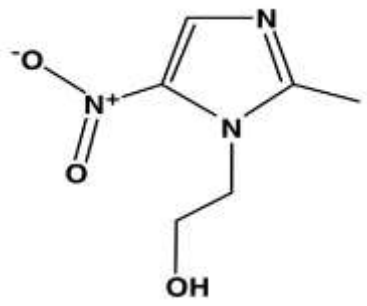

Figure 1: The molecular structure of 5-nitroimidazole

Case

39 years-old male patient with the signs of night sweats, coughing and fever for 6 months, have been referred to internal medicine outpatient clinic. Systemic examination was normal except the hepatomegaly. The patient had a normal anamnesis.

Hepatic ameobiasis cysts were diagnosed via abdominal ultrasonography then metronidazole treatment was prescribed. Aspartate Aminotransferase (AST) level was 70U/L, Alanine Aminotransferase (ALT) level was 140U/L, Immunoglobulin E (IgE) level was 707IU/ml. The patient continued the treatment for 18 weeks. AST level was 54U/L,ALT level was 82U/L, IgE level was 260IU/ml. after treatment (Table 1).

Infectious complaints regressed but bilateral lower extremity formication and burning sensation persisted after 2 months of metronidazole treatment. Peripheral neuropathy was suspected due to the persistence of the signs, then the patient was consulted to the neurology clinic and metronidazole medication was ceased. After ceasing the metronidazole treatment, partial loss of symptoms was observed.

Neurological examination showed that bilateral Achilles deep tendon reflexes (DTR) were absent, bilateral patellar DTRs were hypoactive. Socks type hypoesthesia was examined at both lower extremities. Other neurological findings were normal.

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Table 1: Patient biochemistry table before treatment and after treatment. AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, IgE: Immunoglobulin E

Parameter	Referance Value	Before treatment	After treatment
AST	0 – 35 U/L	70	54
ALT	0 – 34 U/L	140	82
IgE	1-100 IU/mL	707	260

As a result of the electromyography (EMG), symmetrical sensorial axonal peripheral neuropathy of bilateral lower extremities was determined. Following the control examinations, regression of the symptoms and EMG findings were observed.

Discussion

Metronidazole is frequently prescribed in the gastroenterology and gynaecology clinics. It has not been thought to be neurotoxic so far although some case reports present that metronidazole may cause neuropathy (8,9). Metronidazole is administered for hepatic ameobiasis abscess for 7-14 days, and for some other diseases it may be used for a long time period (9).

Cumulative neurotoxic dose of metronidazole reported in the literature is between 13,2 and 228 gram. Development duration of neurological symptoms may vary between 11 days and 6 months (10-12).

In our case, treatment duration was 4 and a half months as there was not a recovery from the disease and neurological symptoms started 2 and a half months ago. Mechanism of the neuropathy is unknown yet but it causes axonal type sensory-motor neuropathy (9), likewise we have stated axonal type sensorial neuropathy in the EMG results.

In another case report which studied the neuropathic side effects of metronidazole, 13 patients between the ages of 12 and 22 were administered metronidazole per os for a period of 4-11 months. The follow-ups presented that 11 patients had neurological symptoms and peripheral neuropathy with decelerated neuronal transmission. Consequently, treatments of 9 patients were suspended then it was observed that 5 of them fully recovered 3 of them almost recovered and peripheral neuropathy of one patient persisted (13).

Turan et al. (14) reported a case with the diagnoses of acute myelocytic leukaemia and vulva abscess that was given metronidazole and developed peripheral neuropathy

Some occasions convinced us that the peripheral neuropathy of the case was a side effect of metronidazole as our case developed peripheral neuropathy without any other diseases, etiological factors or any other medications with side effects those may cause peripheral neuropathy; before the metronidazole treatment there were not any complaints pointing out peripheral neuropathy; complaints started after metronidazole treatment and ceased after suspension of the treatment

Conclusion

As a result, medications of the patients should be primarily checked while searching for the reasons of the peripheral neuropathy. With this case report which developed metronidazole induced peripheral neuropathy, we aimed to state the importance of early diagnosis and treatment because drug induced peripheral neuropathy may be persistent

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of Research/Case, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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A case of Zellweger syndrome accompanied by hypertrophic cardiomyopathy

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Abstract

Peroxisomal biogenesis disorders are a group of genetically and clinically heterogenous disorders which affect very-long chain fatty acid metabolism. Zellweger syndrome (ZS) is a rare, congenital disorder characterized by multisystem involvement including central nervous system, skeletal system, liver, kidney and eyes, due to absence of peroxisomes in the cells. Hypertrophic cardiomyopathy (HCM) is defined as septal or posterior wall thickness that is more than two standard deviations above the mean normal thickness measured by echocardiography. Here we present a newborn with Zellweger syndrome and hypertrophic cardiomyopathy.

Key words: Hypertrophic Cardiomyopathy, Zellweger Syndrome, Newborn

Introduction

Zellweger syndrome (OMIM 214100) is the prototype disorder of a group of peroxisomal biogenesis disorders. Zellweger Syndrome (ZS) is a fatal autosomal-recessive hereditary disease characterized by the reduction or absence of peroxisomes in the cells of the liver, kidneys and brain. The absence of peroxisomes results in impairment of many metabolic pathways, especially beta-oxidation of very long chain fatty acids (VLCFA). In the newborn period, effected children are hypotonic, feed poorly and have distinctive facies, seizures, hepatic dysfunction and renal cysts (1,2).

HCM is defined as septal or posterior wall thickness that is more than two standard deviations above the mean normal thickness measured by echocardiography (3). In the newborn or the fetus, transient hypertrophic cardiomyopathy is commonly attributed to certain maternal metabolic disorders (in particular, diabetes mellitus) or to antenatal or postnatal exposure to steroids. In addition, hypertrophic cardiomyopathy has been described in association with genetic syndromes and, in rare cases, as a primary lesion associated with other congenital heart defects (4). In this report, we present a case of ZS accompanied by hypertrophic cardiomyopath.

Case

A 3110-g female infant was born at 40 weeks' gestation to a 26- year-old gravida 2, para 2, by cesarean delivery. Apgar scores were 7 and 8 at 1minute and 5minutes, respectively, and no resuscitation was required. Her head circumference, weight and length were 35 cm (50th centile), 3110 gr (25-50th centile), and 51 cm (50-75th centile), respectively. Pregnancy was uneventful and fetal growth was normal on follow-up. She was the second offspring of healthy parents with no consanguinity. The first child had died of ZS at 4 months of age. After birth, she was noted to be floppy and required oxygen supplementation and was transferred to the neonatal intensive care unit.

On physical examination the infant had atypical facial appearance with epicantal folds, high forehead and large anterior fontanel (3X4 cm) (Figure1). She had mild tachypnea without retractions, hypotonia and diminished neonatal reflexes. The liver is palpable 2 cm. An ultrasound examination of kidneys showed increased echogenicity and cortical cysts. Cranial ultrasound was normal. Karyotype demonstrated 46,XX.

On 9th day, a grade 2/6 systolic murmur was noted. Mild cardiomegaly and normal pulmonary vascular markings were present on the chest radiograph.

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Figure 1: Facial appearance

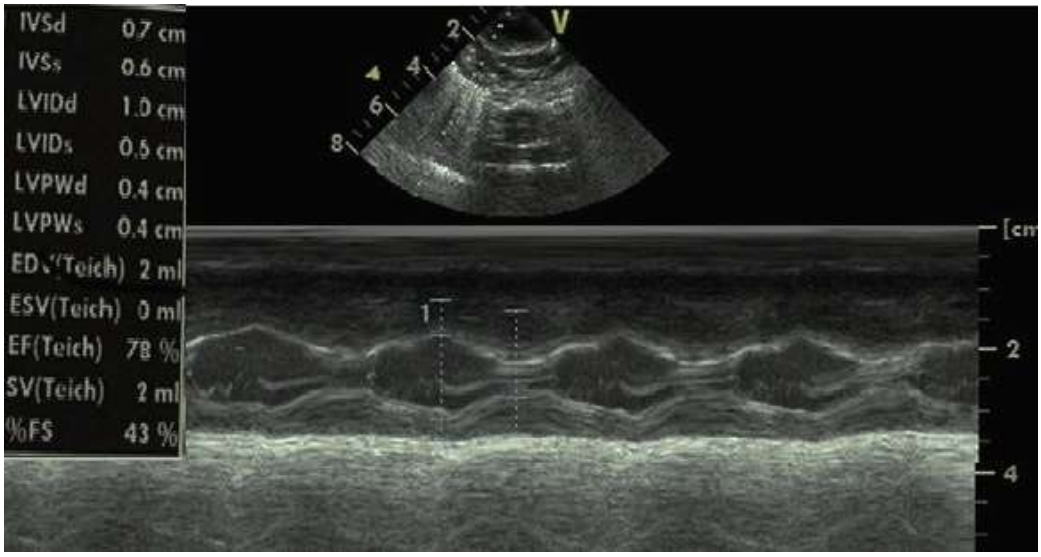

Figure 2: Echocardiography showing interventricular septum thickening (IVSd Z 0.7 cm)

Table 1: Serum levels of VLCFA and phytanic acid

VLCFAs	Patients	Normal Values
C26:0 (µmol/L)	10,10	0,6-1,3
C24:0 (µmol/L)	46,43	37,4-79,4
C22:0 (µmol/L)	35,61	41,1-90,3
C24:C22	1,3	0,68-1,008
C26:C22	0,28	0,011-0,026
Phytanic acid (µmol/L)	1,31	< 5,28

Echocardiographic evaluation showed marked thickening of the interventricular septum (IVS) (0.7 cm) (Figure 2). The family history was negative for hypertrophic cardiomyopathy or sudden death. A maternal drug history was unremarkable and oral glucose tolerance test was normal. The maternal glycated hemoglobin (HbA1c) level was 4.6 %.

Laboratory tests upon admission including complete blood count, peripheral blood smear, C-reactive protein, serum glucose, electrolytes, renal and liver function tests were unremarkable. Tandem mass spectroscopy analysis was normal. The baby was completely asymptomatic all the time.

The infant remained hypotonic with no sucking reflex and was commenced on orogastric tube feeding. Oxygen requirement resolved within 10 days and supplemental oxygen was discontinued. Hepatomegaly was noted on day 12, and bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) started to rise. Laboratory investigations revealed ALT of 307 IU/L, AST of 750 IU/L, total bilirubin of 6.4 mg/dL and direct bilirubin of 3.4 mg/dL.

Phenotypic features, generalized hypotonia, renal cortical cysts and elevated liver transaminases suggested peroxisomal disorders, and VLCFA analysis was ordered which was compatible with Zellweger syndrome (Table 1). PEX1 gene analysis was performed, which showed a previously reported mutation: homozygous p.V100Gfs*32. On day 27 of life she developed aspiration pneumonia and died on day 29 of life following worsening of his respiratory status.

Discussion

Zellweger syndrome is a fatal autosomal recessive disease caused by an absence of functional peroxisomes. Impaired metabolism results in the accumulation of toxic metabolites, which give damage to developing neurons (5). Severe psychomotor retardation, severe hypotonia at birth, dysmorphic facial features and liver dysfunction are the hallmarks of this disease. Central nervous system abnormalities encountered in this disease include cortical dysplasia, neuronal migration defects and dysmyelination. Affected infants usually have small renal cortical cysts. Patients usually die within a few months after birth (5).

Prenatal diagnosis is possible via enzyme assays using chorion villous samples or amniocytes or by analysis of VLCFA in amniotic fluid. If the genetic defect has been identified in the index patient, DNA analysis can be performed (2).

Zellweger syndrome may be accompanied by cardiac anomalies, which include ventricular septal defect, patent ductus arteriosus and aortic arch anomalies (6). Our patient only had hypertrophic cardiomyopathy diagnosed by echocardiography. Hypertrophic cardiomyopathy in infancy has been described as a result of exposure to maternal diabetes or to corticosteroids.

In addition, hypertrophic cardiomyopathy has been described in association with perinatal asphyxia, metabolic diseases, in utero ritodrine exposure, Noonan syndrome, systemic hypertension, and familial HCM (7). In our case, prenatal history was negative for maternal risk factors. Oral glucose tolerance test performed during pregnancy and the postpartum HbA1c level were in the normal range in our patient. Although rare, all newborns with Zellweger syndrome should be evaluated by echocardiography for accompanying cardiac defects.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

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