INTRODUCTION

Epilepsy affects approximately 50 million people worldwide and is defined as a chronic disorder of the brain that is characterized by spontaneous and recurrent seizure activity, which is triggered by the abnormal discharge of neurons ***(Kramer and Cash, 2012).*** Treatment of this neurological disorder deserves special attention. Although anticonvulsant drugs have proven their efficacy, their use has demonstrated considerable side-effects. Furthermore, patients suffer from intractable conditions related to the type of crisis, drug resistance or other factors. Thus, there is a need for the development of new alternative therapeutic tools ***(Lopes et al., 2013).***

Honey is a supersaturated solution of sugars, which contains more than 180 other constituents like enzymes, amino acids and organic acids, carotenoids, Maillard reaction products, vitamins, minerals and polyphenols ***(Gheldorf et al., 2002).***

The minor compounds give the bioactive properties of honey, such as phenols (flavonoids and phenolic acids), and some studies have indicated that these are more potent regarding the antioxidant effect than vitamin C or E ***(Beretta et al., 2005).***

Honey is known to be rich in enzymatic and non-enzymatic antioxidants, including glucose-oxidase, catalase, flavonoids, ascorbic acid, phenolic acids and carotenoids ***(Batrušaityte et al., 2007).*** Naturally, honey has been traditionally recognized as a valuable source of energy. It has also been recognized for its antimicrobial and antioxidant characteristics ***(Alvarez-Suarez et al., 2010).*** Therefore, honey has attracted attention in recent years as a useful or potential substance used in medicine and cosmetics products. The chemical composition of propolis is quite complicated. More than 300 compounds such as polyphenols, phenolic aldehydes, sequiterpene quinines, coumarins, amino acids, steroids and inorganic compounds have been identified in propolis samples ***(Khalil, 2006).***

One established property about honey is that it assists the building and development of the entire central nervous system, particularly among newborn babies and preschool age children, which leads to the improvement of memory and growth, a reduction of anxiety, and the enhancement of intellectual performance later in life ***(Cantarelli et al., 2008).*** Additionally, the human brain is known to undergo postnatal development with the obvious maturation and reorganization of several structures, such as the hippocampus and cerebral cortex. It has been reported that this postnatal development occurs through

neurogenesis, which occurs predominantly during childhood, and this development can also extend into adolescence and even through adulthood ***(Oyefuga et al., 2012).*** Furthermore, honey decreased the number of degenerated neuronal cells in the hippocampal CA1 region, a region that is known to be highly susceptible to oxidative insult ***(Cai et al., 2011).***

Oxidative stress is regarded as possible mechanisms in the pathogenesis of epilepsy. Studies have already verified that status epilepticus changes redox potential and decreases the level of ATP, which can lead to a collapse in brain energy production and supply. Liang and Patel have demonstrated oxidative damage to susceptible targets (protein, lipids, and DNA) caused by persistent seizures (status epilepticus) ***(Liang and Patel, 2006).*** Several studies (animal models and genetic studies) have demonstrated an increase in mitochondrial O&NS and subsequent cell damage after persistent seizures ***(Chuang, 2010).***

Antioxidants are endogenous or exogenous compounds that either reduce the formation of free radicals or react with and neutralize them, thus potentially protecting the cell from oxidative injury. Because the biochemistry of free radical injury is complex, many substances may act as potential antioxidants and thus provide protection against disease or limit its consequences ***(Hamid et al., 2010).***

AIM OF THE WORK

Evaluation of antioxidant effect of honey on pediatric patients with refractory epilepsy.

Chapter 1

EPILEPSY

Definition:

French and Pedley (2008) defined epilepsy as tendency to develop two or more seizures that are not provoked by other illnesses or circumstances, while all patients with epilepsy experience seizures, not all individuals with seizures have epilepsy.

Seizures may be acute symptomatic or unprovoked. Acute symptomatic seizures are seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult. Unprovoked seizures are seizures occurring in the absence of precipitating factors and may be caused by a static injury (remote symptomatic seizures) or a progressing injury (progressive symptomatic seizures). Unprovoked seizures may be single or recurrent ***(Hauser and Beghi, 2008).***

During a seizure, the epileptic activity in the brain can be seen as a series of "spikes" or "spikes and waves" in electroencephalographic recordings. These "spikes" or "spikes and waves" are called the "electrographic" seizure. The behavior of the patient during the epileptic attack is called the

"clinical" seizure. If the clinical seizure involves muscle spasms, it is called a "convulsion" ***(Burnham, 2002).***

Epidemiology of childhood epilepsy:

- ***Worldwide distribution:-***

Age:

Epilepsy is the second most common chronic neurological disorder after stroke affecting approximately 0.5-2% of the population ***(Rajabzadeh et al., 2011).*** It is estimated that 0.5-1% of all children have epilepsy, with the majority presenting during infancy or early childhood ***(Russ et al, 2012).***

Johnston (2008) reported that the cumulative lifetime incidence of epilepsy is 3% and more than half of cases begin in childhood. The annual prevalence of epilepsy is about 0.5-0.8% because many children outgrow epilepsy.

The overall incidence of childhood epilepsy from birth to 16 years is approximately 4 in 10, 000 children per year and after that about 5-7 cases per 10, 000 children per year ***(Oka et al, 2006).***

The incidence in the first year of life is about 120 in 100.000. Between one and ten years of age, the incidence is about 40-50 in 100.000 and then drops in the older ages to about

1% (***Raspall-Chaure et al, 2008).***The incidence of epilepsy over time appears to decrease in children, whereas it increases in the elderly ***(Kotsopoulos et al., 2002).***

Sex:

Some studies found that males are more affected than females, and suggested that females might find it easier to conceal their fits ***(McHugh and Delanty , 2008)***

El-khayat et al., (1994) reported incidence in primary epileptic male: female children of about 1.4: 1 and other studies found almost an equal sex incidence among adults**.**

Race:

No consistent racial differences have been found, though several studies from the USA showed higher incidence and prevalence figures in Afro-Americans than white-Americans which may reflect a poorer standard of perinatal and other health care ***(Oka et al, 2006).***

Socioeconomic status:

The prevalence of epilepsy is usually found to be higher in the lower socioeconomic groups and those living in poverty ***(Elliott et al., 2009).***

Prognosis and mortality:

Epilepsy cannot usually be cured, but medication can control seizures effectively in about 70% of cases ***(Fisher et al, 2005).*** Of those with generalized seizure more than 80% can be well controlled with medications while this is true in only 50% of people with focal seizures ***(Duncan, 2007).*** One predictor of long-term outcome is the number of seizures that occur in the first six months (***Devlin, 2012).*** Other factors increasing the risk of a poor outcome include little response to the initial treatment, generalized seizures, a family history of epilepsy, psychiatric problems, and waves on the EEG representing generalized epileptiform activity ***(Gloss and Vickrey, 2012).*** In the developing world 75% of people are either untreated or not appropriately treated, in Africa 90% do not get treatment, this is partly related to appropriate medications not being available or being too expensive ***(Fisher et al, 2014).***

People with epilepsy are at an increased risk of death. This increase is between 1.6 and 4.1 fold greater than that of the general population ***(Kwan and Patrick, 2012)*** and is often related to: the underlying cause of the seizures, status epilepticus, suicide, trauma, and sudden unexpected death in epilepsy (SUDEP). Death from status epilepticus is primarily due to an underlying problem rather than missing doses of medications. The risk of suicide is increased between two and

six times in those with epilepsy. The cause of this is unclear ***(Hitiris et al, 2007)***. SUDEP appears to be partly related to the frequency of generalized tonic-clonic seizures and accounts for about 15% of epilepsy related deaths ***(Gloss and Vickrey, 2012)***. It is unclear how to decrease its risk. The greatest increase in mortality from epilepsy is among the elderly. Those with epilepsy due to an unknown cause have little increased risk ***(Kwan and Patrick, 2012).*** In the developing world many deaths are due to untreated epilepsy leading to falls or status epilepticus (***Holmes et al, 2008).***

Mechanisms and pathophysiology of seizures:

Although the precise mechanisms of seizures are unknown, several physiologic factors are responsible for the development of a seizure. To initiate a seizure, there must be a group of neurons that are capable of generating a significant discharge and impairment of the γ-aminobutyric acid (GABA) inhibitory system. Transmission of seizure discharge depends on excitatory glutamatergic synapses. Evidence suggests that excitatory amino acid neurotransmitters (glutamate, aspartate) may have a role in producing neuronal excitation by acting on specific cell receptors. Seizures may arise from areas of neuronal death, and these regions of the brain may promote development of hyperexcitable synapses that can cause seizures. Lesions in

the temporal lobe cause seizures, and when the abnormal tissue is removed surgically, the seizures are likely to cease ***(Johnston, 2008).***

Two hypotheses have been suggested to explain the origin of seizures after brain injury. One suggests that inhibitory neurons are selectively damaged and the remaining excitatory neurons become hyper excitable. The other hypothesis suggests that aberrant excitatory circuits are formed as part of reorganization after injury ***(Johnston, 2008).***

Seizures are more common in infants and certain seizures in pediatrics are age specific as infantile spasms; this observation suggests that the underdeveloped brain is more susceptible to specific seizures than is the brain of an older child or adult. This is consistent with basic science data indicating that the immature brain is more excitable than the mature brain, reflecting the greater influence of excitatory glutamate-containing circuits ***(Johnston, 2008).***

Furthermore, the substantia nigra has an integral role in the development of generalized seizures. It has been proposed that the functional immaturity of the substantia nigra may have a role in the increased seizure susceptibility of the immature brain. Additionally, it is suggested that substantia nigra outflow tracts

modulate and regulate seizure dissemination but are not responsible for the onset of seizures ***(Johnston, 2008).***

Different behaviors of the seizures depend on spread of the discharge and which specific cortical or subcortical nuclei developed synchronize discharges. Loss of synchrony and active inhibition lead to ictal termination but not as a result of neuronal exhaustion (***Fred L and Solomon, 2008).***

Onset of epilepsy:

The onset of epilepsy may occur at any time during life. In many individuals, seizure onset occurs in childhood before the age of fifteen. During young adulthood or in middle age, seizure onset is less likely. There is an increased incidence of seizure onsets, after the age of sixty. These late-onset epilepsies may be the result of small strokes ***(Sander, 2003).***

Kandil et al. (2007) in their study of pattern of epilepsy in childhood and adolescence reported that about 70% had age at onset of 5.9±3.5 years.

Risk factors for epilepsy:

While epilepsy is a condition that is not contagious, there are risks associated with developing it. It may follow a stroke, infections of the brain, such as encephalitis or meningitis and in some individuals; especially children, a

high fever can place them at risk for having a seizure ***(Hunt and Inder, 2006).***

Maternal infections during pregnancy have been associated with an increased risk for epilepsy in children ***(Sun et al., 2008***); also prenatal exposure to both preeclampsia and eclampsia was associated with an increased risk of epilepsy in children born after 37 weeks of gestation ***(Wu et al., 2008).***

Factors that are known to increase risk of the epilepsies in children include congenital malformations of the CNS, moderate or severe head trauma, CNS infections, certain inherited metabolic conditions, and genetic factors. However, they account for only 25% to 45% of cases, and thus, the etiology of most cases of the epilepsies remains obscure ***(Cowan, 2002).***

Ehrenstein et al., (2007), on their cohort longitudinal study on Danish children that were followed up for 12 years after deliveries, found that prolonged gestation (postterm delivery), depressed Apgar score at birth, instrument-assisted and Cesarean deliveries are associated with increased risk for epilepsy.

Similar results were obtained by ***Cansu et al., (2007)*** which found that the most important risk factors for epilepsy in their study were abnormal neurological signs, history of atypical febrile seizures, severe head injury and a low Apgar score. Other

important risk factors were moderate head trauma and a history of epilepsy in the family.

Causes of epilepsy:

Epilepsy can be defined in terms of etiology into three types: idiopathic, symptomatic, and cryptogenic. About 30% of childhood epilepsy is idiopathic in which there is no apparent underlying cause and the brain appears to be completely normal. In patients with idiopathic epilepsy, the seizures are thought to be caused by genetic factors (having no identifiable physical cause) ***(Burnham, 2002).***

In the past, most genetic epilepsies have been categorized as idiopathic until a known cause has been isolated ***(Noebels, 2003).*** Actually, there is a probably a genetic contribution to most cases of epilepsy, as if one of a pair of identical twins has seizures, there is a 95% chance that the other twin will also have seizures. Even in cases of symptomatic epilepsy, some patients develop seizures, whereas others do not -suggesting a genetic Predisposition. In some types of epilepsy the genetic factor is strong and inheritance follows simple Mendelian rules, however in most cases of epilepsy the inheritance is multifactorial ***(Burnham, 2002).***

Between 25% and 45% of childhood epilepsy is symptomatic which is caused by known structural abnormalities

or damage in the brain or by an underling disease (having an identifiable physical cause) such as congenital brain malformation, injury or trauma (at birth or later), brain hypoxia, infection with permanent damage, tumor, stroke, or metabolic disorder ***(Buffo et al, 2008).***

In cryptogenic epilepsy where the child's epilepsy is symptomatic, but the underlying cause can't be located and the child usually has developmental delay or abnormal finding on neurological examination. Although the cause of cryptogenic epilepsy is unknown, it is often assumed to be caused by a brain lesion that is not visible on CT scan or MRI. With the improvement in the quality of these investigations the proportion of cases that are defined as cryptogenic has decreased. In other cases, a child whose epilepsy is considered cryptogenic at first is later diagnosed with a metabolic or mitochondrial disease, and the classification changes to symptomatic epilepsy ***(Donner et al., 2006).***

Classification of epileptic seizures:

It is important to classify the type of seizure that may provide a clue to the cause of the seizure disorder and generally is essential for the understanding, correct diagnosis, and satisfactory treatment of the disorders ***(Kini, 2009).***

Johnston (2008) mentioned the international classification of epileptic seizures as follows:

1- Partial seizures

- Simple partial (consciousness retained)
  - Motor
  - Sensory
  - Autonomic
  - Psychic
- Complex partial (consciousness impaired)

Simple partial, followed by impaired consciousness Consciousness impaired at onset

- Partial seizures with secondary generalization

2- Generalized seizures

- Absences (Typical - Atypical)
- Generalized tonic-clonic
- Tonic
- Clonic
- Myoclonic
- Atonic
- Infantile spasms

3- Unclassified seizures.