INTRODUCTION

Vitamin B12 (cobolamin) plays an important role in DNA synthesis and neurological function, Deficiency leads to wide spectrum of neuropsychiatric disorders**. (Robert & David, 2003)**

Vitamin B12 is found only in animal source foods, so intake is entirely dependent on the amount of animal- source foods in the diet, except where foods are fortified with vitamin**. (Allen, 2008)**

Impaired cognitive functioning is associated with inadequate provision of vitamin B12 **(David & Ilsi, 2008),** and also vitamin B12 concentrations were significantly inversely associated with short-term memory. **(Ans et al., 2010)**

Epilepsy is one of the most common chronic neurologic disorders diagnosed in children and adolescents, the vast majority of epilepsies encountered under the age of 15 years are idiopathic developing without any identifiable or suspected cause**. (Dragoumi et al., 2013)**

Defining intractable epilepsy is essential not only to identify up to 40% of patients refractory to pharmacological management, but also to facilitate selection and comparison of such patients for research purposes, The International League

Against Epilepsy (ILAE) proposed a definition of drug-resistant epilepsy as a failure of adequate trials of 2 tolerated and appropriately chosen and used AEDs schedules**. (Shobhi & Khurram, 2011)**

Most children with epilepsy are of normal intelligence. However, a significant subset will have temporary or permanent cognitive impairment**. (Su Jeong, 2012)**

Antiepileptic drugs as carbamazepine affect vitamin B12 level by microsomal enzyme induction **(kumar etal, 2013).**However in other studies there is no change in vitamin B12 level in children who receiving antiepileptics**. (Sener et al., 2006)**

A subnormal concentration of many nutrients and vitamins has been found to be common in patients with epilepsy, Nutrients that may reduce seizure frequency include vitamin B6, Vitamin B12, magnesium, vitamin E, manganese, taurine, and omega-3 fatty acids. **(Gaby, 2007)**

AIM OF THE WORK

The study aimed to estimate serum vitamin B12 level among children with intractable idiopathic epilepsy and find out its relation to seizure control as well as cognitive functions of them.

Chapter 1

IDIOPATHIC EPILEPSY

Childhood epilepsy is a relatively common disorder affecting 1 of every 100 children, and up to one third of these patients demonstrate drug-resistant epilepsy **(Michael Karsy et al., 2016)**

About 30% of childhood epilepsy is idiopathic, it is the epilepsy in which there is no obvious underlying cause, as a structural problem in the brain or any metabolic disorder, It is possible that idiopathic epilepsy caused by abnormalities at the cellular level **(Jallon & Latour, 2005).**

Idiopathic epilepsy syndromes often run in families, and many idiopathic epilepsy syndromes have an associated genetic component **(Gardiner, 2005).**

Classification of Idiopathic Epilepsy: (Anne et al., 2016)

A) Epilepsies of unknown cause of infancy and childhood:

1- Benign infantile seizures (nonfamilial).

2- Benign childhood epilepsy with centrotemporal spikes.

3- Early and late-onset idiopathic occipital epilepsy.

B) Familial autosomal dominant epilepsies:

1- Benign familial neonatal convulsions.

2- Benign familial infantile convulsions.

C) Generalized epilepsies of unknown cause:

1- Benign myoclonic epilepsy in infancy.

2- Epilepsy with myoclonic astatic seizures.

3- Childhood absence epilepsy.

4- Epilepsy with myoclonic absences.

D) Generalized epilepsies of unknown cause with variable phenotypes:

1-Juvenile absence epilepsy

2-Juvenile myoclonic epilepsy

3-Epilepsy with generalized tonic-clonic seizures only

E) Reflex epilepsies:

1-Idiopathic photosensitive occipital lobe epilepsy

A) Epilepsies of unknown cause of infancy and childhood:

1- Benign infantile seizures (nonfamilial)

The 2001 proposal of The Task Force on Classification and Terminology recognized the benign familial and non-familial infantile seizures among the epileptic syndromes**. (Engel, 2001)**

However, the latest report of the ILAE Classification Core Group considered that both groups (familial and non-familial) are identical—they have similar age at onset, as well as similar clinical and electrophysiological features. They differ only in the family history and represent a unique syndrome: Benign infantile seizures **(Roberto et al., 2009)**

The age of onset is in the first 2 years of life, without known cause with excellent outcome, benign infantile seizure is considered the third most common form of epilepsy in the first two years of life **(Caraballo et al., 2003)**

Benign infantile convulsions (BIC) are mostly brief, often clustered convulsions, with normal electroencephalography during the interictal stage.it is associated with normal development and mostly disappear at age of 3years **(Hironori et al., 2005)**

2- Benign childhood epilepsy with centrotemporal spikes BCECTS).

BECTS is an electroclinical syndrome, it is genetically determined, and age-dependent. **(Amarai et al., 2015)**

It considered as the most common childhood epilepsy syndrome which have a benign course, there is also an overlap with more severe forms of idiopathic focal childhood epilepsies **(Reinthaler et al., 2014).**

Age of onset ranging from 2 to 13 years of age with peaks at age of 7–10**. (Sanchez & Loddenkemper, 2012).**

Patients experience partial seizures with orofacial involvement and frequent involvement of one or both hands, as well as of the leg ipsilateral to the affected side of the face. Patients occasionally experience generalized seizures**. (Ibanez - Mico et al., 2012).**

EEG reported high-voltage spikes or spike-and-wave complexes in the centrotemporal region which may spread to the contralateral side **(Park et al., 2015).**

The prognosis is typically very good, with remission of seizures usually occurring two to four years after initial onset and usually before age 16**. (Panayiotopoulos, et al., 2008)** However, in 1–7% of patients with BCECTS, the condition may evolve into more severe syndromes **(Kramer, 2008).**

Most patients with BCECTS experience seizures rarely, and therefore, do not require treatment with antiepileptic drugs, patients with recurrent seizures respond well the treatment. However, some patients do not respond well to the initial drug and may therefore require more than 1 AED to control seizures**. (Park et al., 2015).**

3- Early and late-onset idiopathic occipital epilepsy

Benign childhood epilepsy with occipital paroxysms (BCEOP), initially described by **Gastaut (1982)**, has been classified under the idiopathic, localization-related epilepsies **(Commission on Classification and Terminology of the International League Against epilepsy, 1989)**. However, with the recognition of a distinct entity with an earlier age-at-onset described by **Panayiotopoulos in 1989**, it was proposed to recognize two different syndromes: early-onset benign occipital seizure susceptibility syndrome (Panayiotopoulos syndrome) and late-onset childhood occipital epilepsy (Gastaut type BCEOP) (**Engel, 2001**).

In the early BOEC, the onset is between 1 and 12 years-old, and the main ictal findings are vomiting and/or deviation of the eyes, which can progress to hemi or generalized seizures **(Alves-Leon et al., 2011)**.

There is also a high occurrence of partial status epilepticus that sometimes can be the only clinical event Characteristically, even after the most severe seizures and status, the child is normal after a few hours of sleep **(Ohtsu et al., 2003)**

In the late BOEC, the onset is between 3 and 16 years-old, and the main ictal findings are visual seizures, as elementary

visual hallucinations, complex visual hallucinations and visual illusions, blindness or partial visual loss. (**Di Bonaventura et al., 2005**), and non visual seizures, as deviation of the eyes and oculoclonic seizures, forced eyelid closure and eyelid blinking, sensory hallucinations of ocular movements and pain **(Alves-Leon et al., 2011).**

The EEG findings are similar in both variants, and consist in the majority of high voltage spike-wave complexes in a normal background activity, bilateral and synchronous, over the posterior regions, predominantly in the occipital lobes **(Camfield & Camfield, 2002).**

Carbamazepine may be the drug of choice, although almost all of the classic anticonvulsants (eg, phenobarbital, valproate, benzodiazepines) are effective **(Ferrie et al., 2006)**.

Epileptic seizures spontaneously resolve by the end of adolescence and rarely reoccur **(Polat et al., 2012).**

B)Familial autosomal dominant epilepsies

1- Benign familial neonatal convulsions

We have a high prevalence of neonatal convulsions but epilepsy syndromes in neonates are rare. **(Jallon & Latour, 2005).**

Benign familial neonatal seizures (BFNS) is an autosomal dominant seizure diseases that occure in early infancy, the onset of seizures is in the first days of life and offset usually occurs by a few months of age**. (Heron et al., 2007).**

Seizures occur in healthy neonates who born after a normal pregnancy and normal delivery, without any precipitating factors, Seizures aslo occur during sleep or wakefulness, frequency of seizures is about 3-6 per day mostly with short duration **(Plouin & Anderson, 2005).**

There is a variation in Seizure types; however, it usually start with tonic motor activity and posturing with apnea, ocular symptoms, and other autonomic manifestation, motor automatisms, chewing and focal or generalized clonic movements. **(North et al., 2008)**

Variable patterns were reported in inter-ictal EEG. It may be normal, discontinuous, focal or multifocal sharp waves or epileptiform pattern, and also the ictal EEG may show either focal or generalized patterns. **(Plouin & Anderson, 2005).**

The most commonly used drug to treat this type of seizures is Phenobarbital; it is effective in about 75% of neonates. Valproic acid and phenytoin also are effective in some patients **(Shorvon et al., 2004).**

2- Benign familial infantile convulsions

Benign familial infantile convulsions is an epilepsy syndrome that affect children, who have no other health or developmental problems and developed seizures during infancy. These seizures have focal origin within the brain but may then spread to be generalized.. **(Samuel et al., 2010)**

The condition is inherited with an autosomal dominant transmission. There are several genes responsible for this syndrome **(Baralle et al., 2000**)

The seizures may occur several times a day, often grouped in clusters over one to three days followed by a gap of one to three months**. (Samuel et al., 2010)**

Ictal electroencephalograms show diffuse discharge from the centro-occipital region and normal interictal EEG **(Baralle et al., 2000**).

Treatment with anticonvulsant drugs is not necessary but they are prescribed and are effective to control the seizures. This type of epilepsy resolves after one or two years, and always have a benign course **(Panayiotopoulos, 2005)**

C)Generalized epilepsies of unknown cause:

Idiopathic generalized epilepsies (IGE) are genetically determined and it can affect normal people of both sexes and races. Seizures occurred as generalized tonic–clonic seizures, typical absence seizures and myoclonic jerks alone and in varying combinations and severity **(Mazurkiewicz -Beldzinska et al., 2010)**

Idiopathic generalized epilepsy represent about 10% of all epilepsies, and also about 40% of seizures with tonic-clonic appearance **(Panayiotopoulos, 2005)**

Conventionally, generalized seizures are thought to affect a large number of brain areas, and lead to abnormal activity across virtually the entire brain, however, focal abnormalities occur in this type suggesting of local and selectively impaired brain function**. (Wang et al., 2015)**

1- Benign myoclonic epilepsy in infancy

Benign myoclonic epilepsy in infants (BMEI) is a rare disease which described by Dravet and Bureau in 1981, it is characterized by short, generalized myoclonic seizures that occure in the first 2 years of life in developmentally normal children**. (Stephane et al., 2006).**

Sixty six percent of BMEI occure in males it and represents about 1%-2% of seizures that start in first at 3 years of life with normal neurological and mental state **(Panayiotopoulos, 2005).**

The ictal EEG reported a generalized discharge of polyspikes, polyspike-waves or spike-wave and the interictal EEG is usually normal. Seizures are controlled by valproic acid and ends during childhood which have a good prognosis **(Mangano et al., 2011).**

This type of seizure is characterized by favorable outcome. The myoclonias have disappeared in all reported children. In most of them it continued for less than a year, with the longest duration up to 6 years and 4 months. **(Nicolson et al., 2004).**

2- Epilepsy with myoclonic astatic seizures (Doose syndrome)

Doose syndrome, otherwise traditionally known as myoclonic–astatic epilepsy, was first described as a unique epilepsy syndrome by Dr Hermann Doose in 1970. In 1989, the International League Against Epilepsy classified it formally as a symptomatic generalized epilepsy, and 20 years later it was renamed ‘epilepsy with myoclonic–atonic seizures **(Sarah & Eric, 2010).**

It is characterized by a myoclonic seizure followed by an atonic symptom in continuity. Symmetrical myoclonic jerks of the arms or facial twitching precedes the more or less pronounced loss of tone (atonia). **(Blume et al 2001**).

The EEG may be initially normal, and with progression of the disease will demonstrate brief bursts of 2 to 5Hz spike and wave and polyspike and wave complexes **(Oguni et al., 2001).**

Doose syndrome is historically described as difficult to treat. Multiple anticonvulsant medications as well as less traditional therapies have been reported in the literature for the treatment of Doose syndrome **(Sarah & Eric, 2010).**

Ethosuximide is reported to be one of the more effective standard anticonvulsants, especially when absence seizures are the primary seizure type. Valproic acid and lamotrigine have also been described as beneficial and even, together, synergistic in the treatment of Doose syndrome **(Wallace, 1998).**

3- Childhood absence epilepsy

Absence epilepsy is a common generalized epilepsy in children, It is characterized by abrupt cessation of activities and consciousness impairment, with more or less automatisms, the

typical absence seizure is brief, lasting only for seconds, with no aura or post-ictal defect. **(Weng et al., 2015)**

Childhood absence epilepsy manifested with recurrent typical absence seizures in healthy school-age children, the age of presentation between 6–8 years. This absence seizures are pharmacoresponsive, self-limited disease result in good neurodevelopmental outcome**. (Nickels, 2015)**

Ictal EEG shows sudden onset of 3 Hz generalized spike-wave complexes, while the inter-ictal EEG typically has a normal background**. (Weng et al., 2015)**

valproic acid or ethosuximide are considered the drugs of choice in this type of seizures, which have equal efficacy in controlling the absences by about 75% of children. **(Glauser et al., 2013)**

4- Epilepsy with myoclonic absences

This type of epilepsy affect about 0.5% of epileptic patients, and have a wide range of presentation from the 1st year to early teens. **(Nordli, 2005; Engel, 2001)**

Altered consciousness with associated rhythmic myoclonic jerks and tonic contractions of the limbs are the features of this myoclonic absence. The jerks may be