Introduction

Neuroimaging is one of the most important advances made in the past decade in the management of seizure disorders. Neuroimaging has an important role in the investigation and treatment of patients with epilepsy. Diagnosis of the underlying substrate in a given patient with epilepsy determines prognosis with higher accuracy than electroencephalography ***(Shorvon, 2009).***

Neuroimaging techniques include computed tomography (CT) and magnetic resonance imaging (MRI), although CT has a diminished role for diagnosis. MRI is the most appropriate imaging technique in the initial investigation of patients with epilepsy. MRI is the most sensitive technique for the diagnosis of hippocampal sclerosis, tumors, and malformations of cortical development. MRI is also critical for neurosurgical planning ***(He et al., 2011a).***

NOW Modern neuroimaging techniques have had a major impact on our understanding of epilepsy as they provide an exquisite degree of anatomical resolution and metabolic information about the epileptic lesion and contribute to the proper classification of certain epileptic disorders. They can be very helpful in the localization of the epileptogenic zone and for mapping functional areas of the brain ***(Varghese et al., 2012).***

These modern neuroimaging techniques are the following:

1) Positron emission tomography (PET)
2) Single-Photon Emission Computerized Tomography (SPECT) scanning
3) Magnetic Resonance Spectroscopy (MRS)
4) FUNCTIONAL MRI (fMRI)
5) Magneticoencephalogram (MEG)
6) Diffuse tensor imaging (DTI)
7) Tractography ***(Varghese et al., 2012)***

Aim of the Work

Review of recent advances of indication, advantages & disadvantages of neuroimaging techniques of epilepsy & to put a flow chart for the steps needed to be done in neuroimaging to reach the right diagnosis in the epileptic patient.

Chapter (1)
History of Neuroimaging of Epilepsy

Profound advances in the field of clinical imaging in epilepsy occurred between 1909 and 2009, the century of the International League Against Epilepsy. Initially imaging was carried out with plain x-ray, air encephalography, and angiography, and these techniques had a relatively minor role in epilepsy ***(Shorvon et al., 1994).***

Computerized tomographic (CT) scanning was introduced in 1971, and magnetic resonance imaging (MRI) a decade or so later, and both these technologies had an immediate and far-reaching impact on epilepsy ***(Shorvon et al., 1994).***

In these years, the research focus has turned to Functional MRI, Magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single photon emission computed tomography (SPECT) ***(Shorvon, 2009).***

The two greatest advances in the investigation of epilepsy in the 20th century were the introduction of electroencephalography (EEG) of brain imaging [(CT) and (MRI)] (Table 1) ***(Shorvon, 2009).***

Table (1): A short history of neuroimaging: Three waves of discovery

First wave: x-ray
1895—(November 7) Wilhelm Roentgen discovers x-ray
1901—Roentgen awarded Nobel prize
1918—Air ventriculography (Dandy)
1919—Air encephalography (Dandy)
1925—1st International Congress in Radiology (London)
1927—Cerebral angiography (Egaz Moniz)
1949—Moniz wins Nobel prize (for frontal leucotomy!)
Second wave: computed axial x-ray tomography
1956—Ronald Bracewell, 2-D image in astronomy using Fourier transform
1968—Godfrey Hounsfield produces first experimental CT scanner
1971—EMI installs the first clinical scanner (Atkinsons Morley Hospital in London); first clinical scan was carried out October 1, 1971
1979—Hounsfield and Bracewell awarded Nobel Prize
Third wave: magnetic resonance imaging
1924—Pauli awarded Nobel prize for "exclusion principle"
1952—Bloch and Purcell win Nobel prize for demonstrating MR
1976—Peter Mansfield builds first human MRI scanner in Nottingham and shows first human MR image (a finger)
1980—First experimental whole body scanner constructed (by John Mallard in Aberdeen)
2002—22,000 MRI scanners worldwide; 60 million MRI scans a year
2003—Peter Mansfield and Paul Lauterbur awarded Nobel Prize

(Shorvon, 2009)

EEG predated CT and MRI, and because of this, the classification of epilepsy and of seizures has been based mainly on electroclinical features, rather than etiologic or anatomic features. It is interesting to speculate what would have happened if MRI had preceded EEG; our classifications schemes may today have been very different ***(Shorvon, 2009).***

Plain radiology:

Despite the invisibility of brain tissue, the bones of the skull could be clearly imaged by plain x-ray. Pathologies categorized into two groups: abnormalities of bone and abnormal intracranial calcification. Relevant Bony abnormalities include meningiomas, skull fracture, calcifications, signs of raised intracranial pressure, bony erosions due to tumors or infections, cranial hemiatrophy, pathologic vascular markings in meningioma or angiomatous malformations, congenital cranial anomalies, infectious diseases (notably cysticercosis; less than 1% of tuberculoma are visible on skull radiology), and congenital abnormalities ***(Shorvon, 2009).***

The sensitivity of skull radiology for many of these pathologies is low, and in fact very few patients with epilepsy have an abnormal skull x-ray. Nevertheless, until the 1980s, routine skull x-ray was ordered in all new patients with epilepsy, and not to do so would have been a dereliction of duty ***(Shorvon, 2009).***

Air Encepahalography:

In 1918, Walter Dandy, neurosurgeon at Johns Hopkins hospital, devised the technique of air ventriculography, in which air was introduced by injection into the lateral ventricle, providing sufficient contrast to outline the ventricular system. His first experiments were on infants with gross hydrocephalus. Dandy injected air through the open fontanelles and then subsequently did the same in adults by drilling burr holes in the skull to allow needle injection. In 1919, Dandy then decided to introduce the air

via a lumber puncture and invented what came to be known as pneumo-encephalography (or air encephalography). Initially Dandy replaced the entire cerebrospinal fluid (CSF), but this was so painful that he modified the procedure so as to include less air, which was more tolerable ***(Bull & Fischgold, 1989).***

Jan Sicard in France accidentally discovered lipodolol, as a contrast medium. This was used by Dandy by (1925-1932) giving an insight into the neurosurgical view of epilepsy and the impact of ventriculography ***(Dandy, 1932).***

Dandy recognized 17 categories of "lesions causing epilepsy," a rather curious melange that no doubt reflected advanced neurosurgical opinion of the time: congenital malformation and maldevelopment, either general or focal; tumors; abscesses; tubercles; gummata; aneurysms; syphilis with or without demonstrable gummata or vascular occlusions; areas of cerebral degeneration and calcification; depressed fractures; hamartomata; foreign bodies; injuries from trauma at birth or subsequently (focal or general); connective tissue formation after trauma; atrophy of the brain after trauma; thrombosis and embolism; cerebral arteriosclerosis; and sequelae of obscure inflammatory processes including encephalitis ***(Dandy, 1932).***

Cerebral Angiography:

The next landmark development in the field of neuroimaging was the invention of cerebral angiography. In 1927, the Portuguese neurologist, Egaz Moniz, hit on the idea of using the position of the cerebral vasculature, rather than the ventricular system, to outline abnormalities of brain structure.

Moniz realized that the intravascular injection of radiopaque agents might allow visualization of the vessels ***(Lima, 1950).***

Intracarotid arterial injection was then attempted, and percutaneous arterial injection was carried out without serious incident. After various formulations, Moniz alighted eventually on 25% solution of sodium iodide. In 1931, thorium dioxide (Thorotrast, Testagar and Co., Detroit, MI, U.S.A.), a radioactive compound, was introduced as a contrast medium, and this produced greatly superior opacification. The use of this compound also meant that carotid ligation was not needed, and thus the procedure was greatly simplified. As a result, angiography became adopted worldwide and eventually by all neurosurgical units ***(Lima, 1950).***

Thorotrast is insoluble in water and is taken up by tissue where it may be permanently retained. Its radioactivity was concerning, and by 1937 its safety was being questioned, but it was only 30 years later that it was finally recognized to be the cause of the subsequent development of cerebral tumors. Indeed, as late as 1995, lawsuits were being pursued in the United States by sufferers given Thorotrast in these earlier years ***(Lima, 1950).***

Computarized Tomography (C.T.):

In 1930 CT scanning was discovered, a British electrical engineer Godfrey Hounsfield, who almost single-handedly developed the whole technology. Hounsfield received the 1973 Nobel Prize in Medicine and Physiology for his development of CT scanning, and his Nobel prize lecture provides an insight

into how he approached the work. The brain was a prime organ of study with CT, despite its "invisibility" to plain radiology, and epilepsy too was a beneficiary ***(Hounsfield, 1992).***

On September 8–11, 1975, the reports of CT scanning in large series of patients with epilepsy were presented at the 21st International Congress on Electroencephalography and Epilepsy held in Marseilles. At the meeting, organized by Gastaut, 1,702 patients from seven research groups were reported ***(Gastaut, 1976).***

CT abnormalities were found in about two-thirds of cases. The most lesions were found in 55%, and in 20% of cases CT identified a lesion that had been missed in other examinations and simply suspected on clinical grounds. CT picked up cerebral tumors in 11% of all patients referred to Gastaut and 16% of patients older than 20 years. Gastaut, who was an enthusiast for EEG, wrote even then that CT will be requested as often as EEG in patients with epilepsy. Among the subtypes of epilepsy, the frequency of abnormal CT varied. The most common finding on CT was diffuse atrophy ***(Gastaut, 1976).***

The results of the study of C.T. done over 500 consecutive cases of epilepsy derived from ***(Gastaut, 1976)*** where in 73 patients with primary generalized epilepsy 11% lesions detected on CT, in 74 patients with secondary generalized epilepsy 61% lesions detected on CT, in 198 patients with partial seizures (simple & complex) 63% lesions detected on CT & in 155 patients with unclassified seizures 16% lesions detected on CT.

Young et al. (1982) scanned 220 patients presenting with epilepsy to a neurologic clinic and found abnormalities in 24% overall, but in only 6% of those without focal signs or focal abnormalities on the EEG. He recommended, therefore, that CT should be reserved for patients with focal findings—but the view was challenged on the basis that occasional treatable cerebral lesions will be missed. The typical lesions picked up by CT in epilepsy included: tumors, infection, ischemic cerebrovascular disease, hemorrhage, arteriovenous malformations, and trauma.

Interestingly, with the advent of CT, by 1987, the need for angiography in epilepsy was reduced to about one-third of its previous total, and the need for air encephalography had all but disappeared ***(Shorvon et al., 1994).***

The CT scan is normal in most people with epilepsy. Abnormalities that might be seen are atrophy (shrinking of the brain), scar tissue, strokes, tumors, or abnormal blood vessels ***(Shorvon et al., 1994).***

Like ordinary x-rays, CT scans expose the patient to radiation. However, the amount is low and the procedure is safe even if it needs to be repeated several times. The scanner is a large machine, but less confining for patients than the machine used for MRI ***(Ruben, 2004).***

The advantages of CT scanning include speed and easy availability in most places. It has lower resolution than MRI for

showing brain structures, however, and it is not as good at discriminating between the brain's gray matter and white matter ***(Ruben, 2004).***

Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalised epilepsy has been made ***(Arroyo et al., 2004).***

INDICATIONS OF CT IN EPILEPSY:

CT should be used to identify underlying gross pathology if MRI is not available or is contraindicated, and for children and young people in whom a general anaesthetic or sedation would be required for MRI but not CT ***(Arroyo et al., 2004).***

In an acute situation, CT may be used to determine whether a seizure has been caused by an acute neurological lesion or illness ***(Arroyo et al., 2004).***

Regarding the results reported for adults, there has been a relatively high prevalence (between 34 – 45%) of CT scan abnormalities in adults with a new seizure. As a result, a recommendation has been published to perform emergent neuroimaging in large population of adults having their first seizure ***(Bluvstein & Moshe 2002).***

So far, several studies have reported the prevalence of abnormal neuroimaging in children with new-onset seizures. The prevalence of abnormal neuroimaging in these studies ranged

between 0-21%. The proportion of children with febrile seizures ranged between 17% and 71%. It is important to note that children with febrile seizures, either simple or complex, are at low risk of neuroimaging abnormalities ***(Warden et al., 1997).***

CONTRAINDICATIONS:

Previous exposure to CT for 4 times make it contraindicated for further exposure as it increases the probability of mutations & cancer formation ***(Tepper, 2011).***

Chapter (2):
Structured MRI in Epilepsy

Magnetic Resonance Imaging (MRI):

Just as the practice of neurology was in the process of adjusting to new reality of CT, another technological tidal wave broke over neurology: MRI ***(Kevles, 1997).***

The key contributions of MRI to the clinical practice of epilepsy have been in two main areas: the elucidation of structural etiologies in symptomatic epilepsy, and in refining epilepsy surgery. The impact of MRI in detecting structural etiologies in epilepsy which was a survey of prevalent patients with largely chronic epilepsy who were all considered "cryptogenic" on the basis of normal CT scanning. In 341 prevalent cases of epilepsy only 26% were no abnormalities found, 32% have Hippocampal sclerosis, 13% have cortical dysgenesis, 8% have vascular malformation, 12% have tumors, 6% have infarct/contusion & 11% have other findings. Of course, the yield of MRI in newly diagnosed patients with epilepsy is much lower (approximately 15% showing a causal abnormality), emphasizing that epilepsy is often not a disorder with macroscopic structural change ***(Shorvon, 2009).***

Structural MRI:

Structural MRI has also of course made a huge impact in the field of epilepsy surgery. It would be now unthinkable to carry out epilepsy surgery without prior MRI, and MRI is a leading

modality of presurgical evaluation. Indeed, the absence of abnormality on MRI currently is considered a significant contraindication to surgical intervention. The detection of tumors, vascular lesions, and hippocampal sclerosis opens a potential surgical option for many patients in whom this previously would not have been contemplated. Other important roles for MRI include angiography, intraoperative MRI imaging, and 3-D guidance for resection and depth electrode implantation. MR angiography particularly has become an essential investigation of angiomas and arteriovenous malformations, which often present with epilepsy ***(Shorvon, 2009).***

Increasingly, attention has switched to functional rather than structural MRI techniques, which despite many research efforts and massive funding have yielded currently findings of only very limited clinical importance in the field of epilepsy. Imaging may an inherently inappropriate technology for evaluation of function (in contrast to structure), not least because most brain functions (including epileptic seizures) are not well localized phenomena. Research is often justified as having "potential importance in presurgical localization" or "to localize function," but such presurgical tests need to be validated and their sensitivity and specificity and predictive value established. This is seldom achieved. Equally, the widespread nature of the activation in some Functional Magnetic Resonance Imaging (fMRI) techniques is attributed to a wide "epileptogenic zone," despite the fact that this is a concept impossible to demonstrate in almost all cases and one where definition is entirely circular. The only contemporary

routine clinical role of fMRI currently is to lateralize (but unfortunately not to localize) language and motor function in presurgical evaluation ***(Shorvon, 2009).***

- **Hippocampal Findings in MRI**

Hippocampal sclerosis (HS) was, prior to MRI, possible only to infer by EEG and clinical history, and neither its frequency nor importance in epilepsy were fully appreciated. Up until the 1950s it was commonly assumed to be a consequence of epilepsy, rather than its cause, and found only in severe and chronic cases. The introduction of temporal lobectomy led to a cause versus consequence debate, but it was only when MRI imaging in the 1990s proved to be a way of reliably detecting the condition that its importance was appreciated. Since then, the degree of hippocampal atrophy on MRI has been shown to be related to histologic severity, outcome of surgery, memory functions, and EEG changes ***(Shorvon, 2009).***

Initially MRI used T1 imaging to detect atrophy, and T2 imaging to detect signal intensity, and both measures are still in widespread use. Fluid-attenuated inversion-recovery (FLAIR) imaging was then recognized to improve the yield of T2 imaging, and volumetric scanning allowing quantitation of hippocampal atrophy improved the assessment of hippocampal damage. Ranges of absolute volume are now available, which allow bilateral damage to be detected, even if there is no marked side-to-side difference. MRI has become the gold standard for assessing hippocampal sclerosis, against which all