Cognitive changes following surgery in intractable hemispheric and subhemispheric epilepsy.

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DEPARTMENT OF NEUROLOGICAL SCIENCES

CHRISTIAN MEDICAL COLLEGE, VELLORE

CERTIFICATE

This is to certify that the dissertation titled "**Cognitive changes following surgery in intractable hemispheric and subhemispheric epilepsy** a" is the bonafide original work of Dr. Santhosh G Thomas submitted in partial fulfilment of the rules and regulations, for Branch-II M.Ch. Neurosurgery, Part-II examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in August 2010.

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And to God be the Glory, great things He hath done….

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AIMS AND OBJECTIVES

The aims and objectives of this study are:

I. To study the short term change in the cognitive skills of children with intractable epilepsy after hemispheric epilepsy surgery.

II. To study the longitudinal changes in the cognitive skills of the children with intractable epilepsy after hemispheric epilepsy surgery.

Hypothesis

1. There will be significant short term changes in the cognitive skills of children with intractable epilepsy after hemispheric epilepsy surgery.
2. There will be significant changes in the cognitive skills of children with intractable epilepsy after hemispheric epilepsy surgery in the long-term follow-up period.

Introduction

The word ‘epilepsy’ is derived from the Greek word meaning ‘to seize upon’ or ‘a taking hold of’ (1). ‘Epilepsy’ was earlier defined as two or more epileptic seizures unprovoked by any immediate identifiable cause (2) excluding neonatal seizures that is seizures appearing before one month of age. However, the definition has been modified by the ILAE (International League against Epilepsy). “Epilepsy” is now defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. An epileptic seizure is a transient occurrence of signs and/or symptoms due to an abnormal excessive or synchronous neural activity of the brain (3). Nearly 1 in 20 of the general population would have an epileptic seizure at some time in their lives and 1 in 200 would have epilepsy. The prevalence of epilepsy in India is about 5/1000 and the incidence is about 50/100,000 per year (4). A person is said to have ‘Active Epilepsy’ (AE) if he has one or more epileptic seizures during the last five year period, regardless of antiepileptic drugs (AED) treatment. In India, the prevalence of AE is around 3.83 per 1,000 people, with the prevalence in the urban clusters more than twice that in the rural clusters (6.23 per 1,000) (5).

REVIEW OF LITERATURE

Intractable Pediatric Epilepsy

'Intractable epilepsy' in adults was previously defined a failure to respond to at least two AEDs over at least a two year period (6). A single definition for "intractable" epilepsy cannot suit all situations as definitions of intractability are individualised to the patient. The commonest definition for intractable epilepsy is when seizures continue despite maximally tolerated doses of more than two AEDs, occurrence of an average of one seizure per month for 18 months with no more than a 3 month seizure free period during these 18 months. (7, 8) 'Hemispheric Epilepsy' refers to epileptiform activity in all four lobes of one hemisphere and when it involves more than two lobes of the brain, it is termed 'subhemispheric epilepsy' (7, 9). Although epilepsy is controlled in about 70% to 80% of epilepsy patients with antiepileptic drug (AED) therapy, 20 % to 30% of patients will continue to have chronic seizures (4, 7). Some of these patients fail to respond because their paroxysmal events are not epileptic. Others continue to have seizures because of incorrect treatment due to misdiagnosis of seizure type or misinformation about appropriate therapy. Of these patients deemed to be intractable, approximately 50% are estimated to have surgically remediable epilepsy (7, 10) (Fig 1).

Effect of Intractable Epilepsy on Cognition

The management of children with intractable epilepsy is a major problem in pediatric neurology that requires frequent outpatient visits and multiple ward admissions. Occasionally the children may require intensive care because of status epilepticus with long term periods of

hospitalization. Children with refractory epilepsy are at considerable risk for cognitive impairment (11, 12, 13, 14, 15, 16) as well as school failure (17), behavioural and mental health problems (12, 18, 19, 20) and overall compromised quality of life (21).

The nature and severity of cognitive symptomatology following seizures are probably related to the age of onset of seizures (21). The cognitive symptoms following seizures are either transient or chronic and static or progressive in nature. Currently, a contemporary numerical taxonomy based on the nature, pattern, and severity of evident cognitive complications classifies the cognitive impairment among children with seizures as those with minimal impairment, predominantly memory impairment, and generalized impairment (impaired memory, cognitive speed and execution) (Hermann and Seidenberg, 2007) (22).

Minimally Impaired comprise of approximately half (47%) of the epilepsy subjects. They exhibit the most intact cognition of the three groups. Their performance across several cognitive domains, including language, immediate and delayed memory, executive function, and psychomotor speed domains although impaired is mild.

Predominantly Memory Impaired consists of 27% and exhibit marked impairments in immediate and delayed memory as well as significantly poorer performance in other cognitive domains. Thus, memory is the most striking cognitive abnormality, and occurs in the context of a mild, generalized depression of overall cognitive performance.

Generalized Impairment consisted of 29% of these epilepsy subjects. They demonstrate the poorest cognition across all domains compared and significantly poorer performance across all cognitive domains when compared with the other two groups. The most striking impairments in this group are in the areas of executive function and cognitive/psychomotor

speed. This taxonomy is useful in planning the cognitive rehabilitation that is necessary after the surgical procedures to control intractable seizures.

Risk factors for Intractable Epilepsy related cognitive decline

Risk factors for epilepsy related cognitive decline discussed in literature are numerous and comprise the mere presence of seizures (16), seizure related variables such as age of onset, frequency and/or severity, duration (21), underlying pathology (21), AEDs (12, 16, 17, 20) and various psycho-social factors (19) often called the 'burden of epilepsy' (21).

Frequency of seizures

The pathophysiologic changes that accompany prolonged seizures have been investigated extensively and reviewed (15, 23, 24). Some neurons are highly vulnerable to damage by continuing seizures like those in the hippocampus (CA1 and CA3 areas), amygdala, entorrhinal, piriform and neocortex, septum and thalamus (23). Several animal experiments have been done with regard to effects of recurrent seizures. Holmes (25) and Swann (26) proposed that recurring seizures during early development result in decreased ability of neuronal circuits to learn and store memories. Recurrent seizures thus cause reduced synaptic plasticity, leading to long term cognitive defects. Bailet and Turk (16) assessed the neurocognitive and behavioural performance in children with idiopathic epilepsy, which showed poor performance in cognitive and academic tests. Recent efforts aim to correlate specific deficits with the seizure variables that may have caused them. The variables that could result in decrease in cognitive capacity in patients with epilepsy include

the underlying pathology and the seizures themselves - age of onset, frequency, duration of the disorder, type of seizure and the anticonvulsant drugs (10, 11, 27, 28). Individuals with recurrent seizures have been studied in groups to find out the correlates of poor intellectual function. When inter-group analyses were performed, strong correlates of impaired neuropsychological abilities were a long seizure history, high seizure frequency, and early age of onset (29). When patients with perinatal brain injuries and hemiparesis were grouped together according to the presence of seizures and compared with controls, the frequency of seizures were correlated with lower scores, regardless of degree of injury as seen on brain imaging (30). Airaksinen et al (12) report that the probability of developing epilepsy increases fivefold in severely mentally retarded children compared with mildly retarded children.

Hermann et al (31) found that patients with childhood onset epilepsy performed significantly worse across all cognitive domains compared with controls, including intelligence, language, visuo-perception, memory and executive function. Cognitive compromise was widespread and consistent with the generalised nature of volumetric abnormalities. The presence of recurrent seizures in the developing brain appeared to be associated with an adverse effect on both brain function and structure. Cross (6) pointed out that early onset seizures are associated with poor cognitive outcome and that early surgical intervention, either lobar, multilobar or a hemispherotomy may be associated with improved outcome.

Interictal discharges

As early as 1939, Schwab (32) showed that subclinical epileptiform discharges may be associated with subtle decrements in cognitive function. This finding has been confirmed and given the name Transitory Cognitive Impairment (TCI) by Aarts et al. (11) TCI is found in approximately 50% of the patients who show frequent subclinical interictal discharges on EEG. The finding of TCI establishes that epileptiform activity may impair cognitive function even if unaccompanied by overt seizure activity. Epileptic EEG paroxysms such as those related to a single spike and electrical status epilepticus during slow-wave sleep (ESES) can produce transitory cognitive impairment, with neuroanatomical specificity between the site of the epileptic focus and the impaired cognitive tasks. It has been reported that a local increase of slow-wave activity (SWA) during sleep after learning is associated with improved performance of the learned task after sleep (33). ESES interferes with the local SWA and impairs the local plastic changes associated with learning and other cognitive functions. The duration of ESES and the localization of interictal foci determine the degree and type of cognitive dysfunction (33). When frequent epileptiform EEG discharges persist over years, they result in effects on stable aspects of cognitive function such as educational achievement and intelligence. The clinical significance is that early detection and treatment of these EEG discharges may prevent a negative impact on cognitive and educational development.

Antiepileptic drugs

Drug treatment has been the principal therapy for epileptic seizures since the introduction of bromide in 1857. At present about 80% of patients with epilepsy have good seizure control on AEDs. These results are usually achieved without serious adverse effects

on cognition, particularly if the seizures are controlled with one drug and blood serum levels are within the recommended range (34). The main cause of cognitive impairment in epilepsy is still under research, but three factors clearly are involved: etiology, the seizures, and the "central" side effects of drug treatment (14). Although the severity of cognitive side effects is generally considered to be mild to moderate for most AEDs, all commonly used AEDs have some impact on cognitive function. Such mild impact may be amplified in specific conditions and may become substantial in some patients when crucial functions are involved, such as learning in children or driving skills in adults or when already vulnerable functions like memory are impaired. The effects may increase with prolonged therapy, which contributes to the impact on activities of daily living in refractory epilepsies (14, 35).

Most antiepileptic drugs, with the exception of the benzodiazepines (which themselves adversely affect cognition) and lamotrigine, do not suppress inter-ictal discharges. Well-designed clinical trials of the effects of antiepileptic drugs are difficult to perform. An ideal drug should control both the seizures and inter-ictal discharges. This can actually improve the cognitive function provided the drugs themselves do not have a cognitive penalty. Williams et al (36) report that there are no adverse effects on cognition from AED monotherapy during the first 6 months of therapy. The risk of AED cognitive side effects is increased with polypharmacy and at higher dosages and higher AED blood levels. Slow titration during drug initiation could reduce these effects (37).

Who is a candidate for surgery?

When epileptic children are deemed intractable, they are evaluated by the presurgical laboratory. The evaluation includes a study of the seizure semiology, neurological

examination, multiple electroencephalogram (EEG) examinations (video telemetry), magnetic resonance imaging (MRI) and neuropsychological evaluation. The focus of the examination is to identify a surgically remediable epilepsy syndrome with good electro-clinico-radiological concordance. If the lesion that is producing epilepsy can be safely removed without incurring deterioration in the functional status, the patient is considered for epilepsy surgery. However if there is no concordance in investigations in the presurgical laboratory evaluation, the patient enters a Phase II evaluation which may include prolonged invasive EEG monitoring, nuclear medicine studies [positron emission tomography (PET) and single photon emission computerized tomography (SPECT)] and a WADA (Sodium amylobarbital) test. Surgery is offered if concordance is obtained and the risk of incurring functional deterioration is considered minimal or acceptable (7).

Surgically remediable pediatric epilepsy syndromes

The surgical treatment of pediatric epilepsy is better understood by subdividing this group based on their location and extent into four subgroups: Hemispheric, Sub hemispheric, Focal and Multifocal (7, 9, 38, 39). In each subgroup, the etiologies may be of congenital or acquired origin.

Etiology of Hemispheric / Subhemispheric Epilepsy

a) Congenital

- Infantile Hemiplegia Seizure syndrome
- Hemimegalencephaly

- Hemispheric Non Hypertrophic Migrational Disorder
- Sturge Weber Disease
- Tuberous Sclerosis

b) Acquired

- Rasmussen Encephalitis
- Sequelae of childhood vascular insults (ischaemic or haemorrhagic)
- Sequelae of meningoencephalitis
- Sequelae of trauma

Hemispheric epilepsy

The most common pediatric hemispheric epilepsy syndromes (both acquired and congenital) are described below.

Infantile hemiplegia Seizure syndrome (IHSS):

IHSS is a descriptive term that refers to unilateral paralysis noticed in early childhood as a result of various pathologies affecting one hemisphere in utero or peri-natally. Two-thirds of the patients affected will develop seizures at some time during childhood, which may be refractory to antiepileptic medication and lead to progressive developmental retardation. Imaging reveals hemispheric atrophy with a dilated asymmetric ventricular system (Fig 2). There may be evidence of middle cerebral or internal cerebral artery infarction and/or associated porencephalic and subarachnoid cysts (7, 9, 38, 39)**.**

Rasmussen's encephalitis (RE):

This is a chronic childhood encephalitis manifesting with intractable epilepsy and progresses almost always to hemiplegia and cognitive dysfunction. 50% of patients have a preceding viral illness, though a clear viral etiology has not been documented. An autoimmune basis has also been suggested (7, 9, 38, 39). These patients typically present with focal motor seizures though other forms are also known and half of these patients eventually progress to epilepsia partialis continua (59). Though this illness is typically unilateral, there have been sporadic reports of bilateral disease. Radiological and functional imaging reveal the slowly progressive unilateral destructive nature of the disease (Figs 3, 4).

Sturge Weber Syndrome (SW):

Patients with SWS (encephalotrigeminal angiomatosis) usually present with progressive hemiparesis, seizures and mental retardation. Radiological studies show the pial angiomatosis and intracranial calcifications (Fig 5). Both localised and diffuse forms of the disease are known but they are almost always unilateral. Patients with focal disease may have normal intelligence and may be candidates for localised resections. On the other hand, diffuse hemispheric SWS often progresses rapidly to marked developmental retardation, which is related to damage to the hemisphere of venous origin (7, 9, 38, 39)

Disorders of neuronal migration:

Hemimegalencephaly (HM) is a hypertrophic neuronal migrational disorder that present with an early onset of seizures, mental retardation, hemiparesis and frequently hemianopia. They can present with a large head and may be associated with linear nevus sebaceus or chronic linear nevi. Radiological imaging shows a markedly enlarged hemisphere with a thickened cortical mantle (Fig 6). On pathological examination, pachygyria is seen and typical microscopic

features include loss of cortical architecture, giant neurons, neuronal heterotopia and gliosis. On the other hand, diffuse hemispheric non-hypertrophic cortical dysplasia occurs less frequently and manifests with a smaller hemisphere with a variety of migrational abnormalities (7, 9, 41, 42)

Other hemispheric syndromes:

A variety of acquired pathologies can affect predominantly one hemisphere. These include cerebrovascular accidents due to thromboembolic phenomena due to heart disease or children undergoing heart surgery or extracorporeal membranous oxygenation. In developing countries, post meningoencephalitic sequelae form a common cause for hemispheric epilepsy. Cerebral infarction secondary to severe dehydration and severe hypotension can also present likewise. Cranial traumas, brain damage secondary to massive intracranial AVM bleeds are more infrequent causes (7, 9, 38, 39)

Selection criteria for hemispheric epilepsy surgery (7, 9, 39)

1. Medical intractability is an absolute requirement but long trials of anti convulsants may not be necessary as most often the seizure frequency is very high. Also some etiologies like Rasmussen's encephalitis, Sturge Weber syndrome and Hemimegalencephaly are known to almost always have intractable epilepsy.
2. Contralateral hemiparesis should be present. Patients with hemispheric epilepsy usually present with weakness of distal musculature of the upper and lower limbs. An examination shows marked weakness of "finger opposition" and inability to do "foot tapping". The power in the proximal musculature is quite good. If hemispherectomy is done prior to maximal hemiplegia (Grade 0/5), digital dexterity and foot tapping may be lost but the patient will be

able to walk and use proximal muscles of the upper limb. In rare cases, this loss of function may have to be accepted as the cost of control of debilitating seizures and cognitive decline

3. Neuro-developmental retardation is usually present due to the interference of frequent seizures on the developing normal hemisphere. However patients with severe neurodevelopmental retardation are not good candidates for surgery though the "good" hemisphere might be anatomically normal. A thorough neuropsychological evaluation to establish base line data and document integrity of the "good" hemisphere is essential prior to surgery.
4. The hemisphere contralateral to the hemiplegia should be demonstrated by radiological [MRI/computerised tomography (CT)] and functional (scalp EEG / EEG video telemetry) imaging to have a unilateral diffuse abnormality. More importantly the remaining hemisphere should be normal to have a good result following surgery. Spread of epileptiform discharges to the normal hemisphere on EEG or even rare independent discharges on the normal side do not imply a poor response to surgery.

Evolution of Disconnective Surgery

The treatment of epilepsy in the 14th century was based mainly on myth and superstition. Epilepsy surgery evolved in 19th century Britain and Europe with the experimental work of Fritsch (1828-1891) and Hitzig (1838-1907). The classic 1886 paper of Victor Horsley heralded the modern era of epilepsy surgery and the introduction of EEG provided a practical means for localizing epileptogenic abnormalities for resection (42).

Anatomical hemispherectomy was first introduced for the treatment of diffuse infiltrating gliomas by Walter Dandy between 1923 and 1928. However, McKenzie was the first to

perform hemispherectomy for infantile hemiplegia and epilepsy in 1938. Krynauw (1950) reported the first series of 12 patients with infantile hemiplegia who underwent anatomic hemispherectomy for hemispheric disease and epilepsy (443. In1961, White, in a review of the literature on hemispherectomy for infantile hemiplegia, reported 6.6% postoperative mortality in a total of 267 patients (44). Following this, concerns about late complications of anatomic hemispherectomy were raised. Oppenheimer and Griffith (1966) described three of 17 patients with recurrent episodes of encephalopathy, obstructive hydrocephalus and superficial cerebral hemosiderosis 3–11 yr following hemispherectomy leading to death (45). Rasmussen (1983) also described intracranial hypertension due to hydrocephalus in 11 of 31 patients, 4.5–24 yr following this surgery. He attributed this to the extent of resection of the hemisphere and its coverings (46). To reduce complications, changes in surgical technique evolved to include subtotal resection, functional hemispherectomy and a hemidecortication (Carson et al., 1996) (47). Functional hemispherectomy which was introduced by Rasmussen and Villemure evolved into hemispherotomy by 1995. Villemure and Mascott in 1995 described a technique 'peri-insular hemispherotomy' (PIQ) which resulted in shorter operative times and fewer early postoperative complications and bleeding. Seizure control was comparable to anatomic hemispherectomy but morbidity and mortality rates were lower (39, 48, 49). Variants of this approach include hemispheric deafferentation, trans opercular hemispherotomy and trans sylvian keyhole functional hemispherotomy (50). The other approach described is the Vertical hemispherotomy approach of Delalande (51).

This went on to evolve into disconnective surgery for subhemispheric epilepsy. A peri-insular posterior quadrentectomy (PIPQ) was first described in 2007 by Daniel and Villemure (9) which is a technical variant of multilobar resection with comparable seizure rates with lower mortality and morbidity.

Peri Insular hemispherotomy

Peri-insular hemispherotomy is a surgical method of functional hemispherectomy. It enables disconnection of the hemisphere through a peri-insular approach requiring only removal of the fronto–parieto–temporal opercular cortices (Fig 7). It follows the same surgical principle of "anatomical subtotal removal of the hemisphere and complete disconnection". It is a radical hemispheric tractotomy based on the concept of maximum disconnection with minimal excision. It resulted from the demonstration that the hemisphere could be disconnected, made nonfunctional, through very small removal of brain tissue (39). The complications–benefits ratio have been clearly documented and confirm that this surgical methodology of hemispherectomy provides excellent seizure outcome, with a low incidence of side effects or complications. The epilepsy outcome is identical to any other method of hemispherectomy, as physiologically, it eliminates the influence of the whole hemisphere. The outcome is not, then, only technique dependent but results, in a great part, from the anatomical substrate responsible for the epilepsy (39, 50).

The seizure outcome after surgery is classified according to Engel's classification. (7)

1. Class I includes the ones who are completely seizure free in the year after surgery.

2. Class II includes ones with rare seizures only (> 90% reduction in seizures)

3. Class III with the ones who would continue to have seizures but have shown worthwhile improvement (75-90% reduction in seizures)

4. Class IV included those who had no improvement or became worse after surgery

Sub hemispheric Epilepsy

Multilobar surgeries (resective or disconnective surgery) have been increasingly used in the last 10 years though these surgeries amount to less than 5% of all epilepsy surgeries (26, 52). When the epileptogenic zone encompasses large areas of the temporal, parietal and occipital lobes and spares the central and frontal areas, multilobar surgery is indicated (Fig 8). The decision for this surgery is dependent on good concordance between the imaging (MRI, CT, nuclear studies), EEG, clinical and neuropsychological evaluations and a clear localization of the lesion to the unilateral affected region (9, 38). The indications for multilobar resections are the same as for hemispheric epilepsy, the pathology being more localized to involve a part of the hemisphere. The presence of residual voluntary motor function of the contralateral distal musculature, i.e. finger opposition and foot tapping is the indication for multilobar surgery preserving eloquent uninvolved cortex (9, 38).

Posterior quadrantic epilepsy surgery

A posterior quadrantectomy is indicated in patients with subhemispheric epilepsy. Once the decision to surgically treat posterior quadrant epilepsy is made, the surgery is tailored to encompass the whole epileptogenic lesion and to avoid the central region, which is still functional. The primary motor and sensory cortices are identified and recognized from scrupulous study of the MRI and correlation with intraoperative surface anatomy, based on gyral pattern, arteries, and veins. The identification of the functional cortex is also aided by electrophysiological means under general anaesthesia before the resection/disconnection. This identification maximizes both the extent of resection and the safety of surgery (9, 26, and 38). In this technical variant, there is minimal removal of brain tissue but complete

disconnection of the remaining major part of the abnormal cortex, which is left anatomically intact and viable by preservation of the arteries and veins irrigating these lobes. In this variant, the temporal lobe is disconnected instead of temporal resection followed by a parieto occipital disconnection and mesial temporal resection (9, 26, 38) (Fig 9).

Timing of surgery

The effects of seizures, anticonvulsants, post ictal state and interictal discharges on cellular events during cerebral maturation in a child with intractable epilepsy is deleterious to the normal maturation of the brain. In addition, the development of regions of the brain that are uninvolved by disease, does not reach its true potential due to disturbed social integration and loss of schooling. At the same time, neurological worsening after epilepsy surgery is a possibility. The chances of neurological worsening after surgery in children is lowered because insults sustained in utero or in childhood stimulate the development of brain functions in the normal hemisphere. There has also been evidence to support that in cases where the seizures started later in childhood, early surgical intervention helps the shift of functions especially language to the contralateral side. However, the exact age at which the normal plasticity of the brain ceases to transfer brain functions has not yet been defined. In view of all these factors, early surgery is advisable in cases of catastrophic childhood epilepsy especially in certain syndromes that are known to progress to intractable epilepsy and developmental retardation (Rasmussen's syndrome and Sturge Weber syndrome). In some cases, if the deficits are not maximal, it may be better to wait till they do become maximal (7, 9, 38, 39, 48, 50)

Cognitive Outcome of surgery

Neuropsychological assessment in children as well as in adults is an important step before and after surgery. Yet, in literature, data about pre- and postsurgical neuropsychological evaluations in children are very few. The first goal of pre- and postsurgical neuropsychological assessments in children is the evaluation of cognitive development (development delay, stagnation, or deterioration), and second, to look for the possible effects of both brain injury, epileptic disorder, and chronic treatment with antiepileptic drugs (AED). Also relevant is the evaluation of selective deficits in specific cognitive competence to localize functional deficits related to the site of lesions or epileptic focus so as to define the candidates for surgical option and the indication of surgery timing. Moreover, it allows the identification of the functional consequences of surgical procedure and, possibly, to single out some predictive factors of cognitive development. The evaluation of cognitive development, and of behavioural as well as emotional features, in children with epilepsy needs the administration of age-appropriate (from infancy to adolescence) and standardized tests.

Neuropsychological assessment in children is peculiar. Indeed, the "child brain", on which pathological conditions such as brain injury and epilepsy operation, is different from the "adult brain" because of maturational and reorganization processes (7, 53). Cognitive performance are, in most patients, below average before surgery and often show regression secondary to frequency of seizures. General brain disturbance may result from frequent seizures, but focal interference of seizures can also be deleterious, particularly, toward language development It is surprising to find that despite complete seizure control, the postoperative evolution of the developmental quotient does not follow a standard positive pattern. Without there being clear explanations, it appears that some patients will show more

improvement in cognitive functions than others. Even if improvement does not occur, deterioration is usually stopped, and once seizures are controlled, the brain is in the optimal condition to manifest its whole psychosocial development potential (7, 39, 42, 54). The plasticity of the brain and the nociferous effects of frequent uncontrolled seizures, antiepileptic medications (at high doses) on the developing brain; social stigma of the disease and the lost time at school makes treatment of this condition a priority (7, 9).

Although there has been varying reports of significant outcomes in the cognition of these children after surgery, there is paucity of literature in this area warranting further studies. This study was designed and conducted to add information to the existing literature in this area of neurosurgery that improves the quality of life of these children.

MATERIALS AND METHODS

Research design

A prospective, longitudinal research design was used to document the changes in the cognitive ability of children with intractable epilepsy following hemispheric epilepsy surgery. The assessments were done during the pre-surgical period evaluation and follow-up period every year for three years.

Study Settings

The study was conducted in the Department of Neurosurgery as well as Child and Adolescent Psychiatry Unit, Christian Medical College, Vellore, Southern India. Christian Medical College is a tertiary care, teaching referral hospital. Patients from all regions of the country and neighbouring countries benefit from these facilities in the hospital.

The Department of Neurological Sciences was founded in 1949 when Dr Jacob Chandy completed his training in Neurosurgery at the Montreal Neurological Institute (MNI), Canada. This was the first such department in South Asia and its structure is modelled after MNI. The Section of Neurosurgery caters to the complete range of major and minor neurosurgical operations such as for brain tumours, vascular diseases such as aneurysm, AVMs, congenital anomalies, spinal disorders and functional procedures. Neurosurgery has 15 operating room full day sessions per week with over 1500 neurosurgical procedures performed every year. Our department has been a pioneer in the field of epilepsy surgery, stereotactic surgery and radiosurgery in the country. The presurgical evaluation and all surgical procedures related to this study were performed in the department.

The Child and Adolescent Psychiatry unit of the Department of Psychiatry has two divisions, one for the children with developmental disorders and the other one for children with emotional as well as behavioural problems. The division for the developmental disorders has twenty-four beds for residential care and equal number of children attend the assessment as well as therapies on a daily basis. The cognitive assessment of children is carried out by a multidisciplinary team with rehabilitation psychologists playing the pivotal role in these assessments. All cognitive assessments for this study were carried out in this setting. Participants from this centre were recruited during the years September 2005 to March 2009 using specific selection criteria.

Study population

The population in this study was children with intractable epilepsy enrolled for hemispheric epilepsy surgery in the Department of Neurosurgery. Those participants who satisfied the selection criteria formed the study sample.

Sample size

Sample size was calculated using the following formula

$$N = \frac{\Pi \{Z_{(1-\alpha/2)} + Z_{(1-\beta)}\}^2 \times \sigma^2}{3 \times \delta^2}$$

The most commonly used values for significance level and power are

($\alpha = 5\%$ and $1-\beta = 90\%$), $Z_{(1-\alpha/2)} = 1.96$ and $Z_{(1-\beta)} = 1.28$

The required number is N. In order to have a significant level of 5% and to have a 90% chance of deducting a mean difference IQ/DQ score of 10 (based on similar previous studies) with a standard deviation of 15, the calculation is as follows:

$$N = \frac{3.14 \times \{1.96 + 1.28\}^2 \times 15^2}{3 \times 13^2} = 14.6 = 15$$

N= 15, If there is a 10% loss to follow up, then

n= N / 1-(10/100) = 15 / 1- 0.1 = 16.66 = 17 → n= 17

Sampling technique

Purposive sampling was used to select the study samples. Samples that fulfilled the selection criteria were included for the study till the required sample size of 16 was recruited. Same children and adolescents were followed up post-surgically with their pre-surgical details as the baseline data for control comparison.

Selection Criteria

Inclusion criteria

1. Children ≤ 18 years of age (UNICEF, 1992).

2. Intractable epilepsy who have been deemed as surgical candidates for hemispheric/subhemispheric disconnective surgery. (Intractable epilepsy is defined as seizures which continue despite maximally tolerated doses of more than two AEDs, occurrence of an average of one seizure per month for 18 months with no more than a 3 month seizure free period during these 18 months).

Exclusion criteria

1. Children with epilepsy whose seizures are controlled with antiepileptic drugs.
2. Children with epilepsy who do not have clinico-electrophysiological-radiological concordance as per presurgical evaluation for disconnective surgery.
3. Informant living with the child for less than 3 months.
4. Families that refused consent for the study.

Measures

The ***Binet Kamat Scale of intelligence*** (Kamat, 1967) is the Indian adaptation of the 1934 version of Stanford-Binet Scale of Intelligence. Some of tests, items and materials were amended to suit Indian conditions, such as Indian coins, typically Indian pictorial scenes, vocabulary and Indian concepts. The intelligence scale assessed the child's skills in six areas: memory, language, conceptual thinking, reasoning, numerical reasoning, visuomotor coordination and social intelligence.

Gesell's Developmental Schedule (Gesell, 1940) gives the developmental skills in four areas: motor behaviour, adaptive behaviour, language & personal as well as social behaviour.

Vineland Social Maturity Scale (Doll, 1965) (VSMS) in eight areas: self help general, self help dressing, self help eating, socialization, self direction, communication, locomotion and occupation. An experienced psychologist assessed the adaptive behaviour of the children during the first and twelfth week of the therapy program.

Interview and assessment

Consecutive children who were diagnosed to have intractable epilepsy from the epilepsy clinic and satisfied the selection criteria were recruited for the study. After the decision was made to help the child with hemispheric epilepsy surgery, the child with the primary caregiver was referred to the Child and Adolescent Psychiatry Unit for the pre-surgical assessment of various cognitive domains. An experienced Rehabilitation Psychologist with a postgraduate qualification and 22 years of experience in assessing the cognitive functioning in children with and without disability administered the Gesell's Developmental Schedule or Binet-Kamat Scale of Intelligence to the child and Vineland Social Maturity Scale to the caregivers. The protocol, which required approximately 2-4 hour to complete, consisted of two sections: (i) a face-to-face interview with both open ended questions and fixed response items on seizures, medication and demography (assessed by the primary investigator); as well as (ii) the cognitive assessments and adaptive behaviour assessment (assessed by the psychologist). All cognitive assessments for this study was carried out in this setting by a single rehabilitation psychologist to avoid inter-rater reliability related issues.

Intervention

The presurgical evaluation includes a study of the seizure semiology, neurological examination, multiple electroencephalogram (EEG) examinations (video telemetry), magnetic resonance imaging (MRI) and neuropsychological evaluation. The focus of the examination is to identify a surgically remediable epilepsy syndrome with good electro-clinico-radiological concordance. In this group, peri-insular hemispherotomy was performed on patients who had hemispheric epilepsy. It allows disconnecting the hemisphere through a peri-insular approach requiring only removal of the fronto–parieto–temporal opercular cortices. It is a radical hemispheric tractotomy based on the concept of maximum disconnection with minimal excision . A peri-insular posterior quadrantectomy is indicated in patients with subhemispheric epilepsy. The surgery is tailored to encompass the whole epileptogenic lesion and to avoid the central region, which is still functional. There is minimal removal of brain tissue but complete disconnection of the part of the abnormal cortex, which is left anatomically intact and viable by preservation of the arteries and veins irrigating these lobes. In this variant, the temporal lobe is disconnected instead of temporal resection followed by a parieto occipital disconnection and mesial temporal resection.

Ethical issues

The ethical concerns of this study were addressed using the following measures:

1. Written informed consent from the primary caregiver (appendix A) for participating in the study and verbal assent from the child for participating in the study whenever possible was obtained ensured voluntary participation.

2. Reversible anonymisation as well as restricted access and disclosure of the obtained data ensured the privacy of patients.
3. The local Institutional Review Board of Christian Medical College had reviewed and provided approval for the study.

Data analysis

As the attrition of patients over the three year follow-up period was more towards the third year it was decided to have an intention-to treat-analysis based approach for the outcome post surgically. To enable the intention-to treat-analysis, the last-observation was brought forward to provide data for attrition.

Statistical Analysis

As part of the data analysis, preliminary checks of skewness verified that our data were suitable for non-parametric analysis. The analyses were carried out at three levels.

Firstly, the descriptive statistical analyses included mean and standard deviations for describing the participants' characteristics was done. Secondly, Chi-square test with Yates correction and Mann-Whitney U test were used to compare the pre and post-surgical data on cognitive variables. Finally, based on the results of the first two level of analyses and review of literature a small number of variables related to cognitive gain were fitted to a logistic regression model that could best predict cognitive gain. Multiple regression yielded regression coefficient for continuous variables, whereas, logistic regression yielded Odds ratio [OR] and 95% confidence interval for the dichotomized main outcome variable of

mental age. A significance level of 0.05 and 2-tailed tests were used unless otherwise noted because of the nature of the study hypotheses. Data was analyzed using the software package of SPSS (version 16).

RESULTS

Table 1: Sample Characteristics

	Whole group N=16	RE (N=9)	IHSS (N=2)	SW (N=3)	HM (N=2)
Males	10 (62.5%)	5	1	2	2
Females	6 (37.5%)	4	1	1	
Right sided lesions	8 (50%)	3	1	2	2
Left sided lesions	8 (50%)	6	1	1	
Age of seizure onset (years)	3.4 (3.6)	5.5 (3.5)	1.5 (2.0)	0.5 (0.0)	9 days
Duration of seizures (years)	6.9 (15.4)	2.6 (2.5)	1.9 (0.1)	4.9 (5.1)	4.4 (0.5)
Status Epilepticus	4	4			
Epilepsia Partialis Continua	6	6			
Loss of schooling (years)	1.2 (1.4)	1.7 (1.4)		1.3 (1.5)	
Mean no of AEDs (pre op)	3.0	3.2	2.5	2.6	3
Follow up in months	20.8 (9.9)	24.3 (10.9)	25.5 (0.7)	13.6 (1.5)	11.0 (4.2)
Mean no of AEDs at follow up	1.1	0.8	0	1.3	3.0

A total of 16 patients underwent disconnective epilepsy surgery for hemispheric / subhemispheric epilepsy from September 2005 till March 2009. Their ages ranged from 8 months to 159 months (mean age =79.13 months ; 6.6 years). There were 10 (62.5%) males and 6 (37.5%) females. The etiology of epilepsy were Rasmussen's encephalitis (n=9 , 56.25%), Infantile hemiplegia seizure syndrome (n=2 , 12.5%), Hemimegalencephaly (n=2 , 12.5%) and Sturge Weber syndrome (n=3, 18.75%). 14 (87.5%) of them underwent peri-insular hemispherotomy for lesions causing hemispheric epilepsy and 2 (12.5%) underwent peri-insular posterior quadrentectomy for lesions causing sub hemispheric epilepsy. 3 (18.75%) patients were followed up for 3 years, 4 (25%) patients were followed up for 2 years, 9 (56.25%) were followed up for 1 year.

The mean age of seizure onset was 3.4 years (range: neonates- 11.5 years). The mean duration of epilepsy was 3.2 years (range: 3 months – 10.5 years). 11 of them (68.7%) were on more than two antiepileptic drugs . The mean AEDs pre op was 3.0 which reduced to 1.1 after surgery. The mean loss of schooling due to seizures was 1.2 years. Children with IHSS and HM were too small to go to school. 15 children (93.75%) had Engel's Class I outcome or complete seizure freedom and 1 child had Class II (> 90% seizure reduction) outcome.

Table 2: Outline of Cognitive domains of the sample (pre op)

Characteristic	Mean (SD)
Mental age (months)	48.2 (31.1)
IQ	67.0 (14.5)
Language (months)	40.6 (2.8)
Meaningful memory (years)	5.7 (1.5)
Non meaningful memory (years)	5.7 (2.2)
Conceptual thinking (years)	8.0 (1.7)
Non-verbal thinking (years)	6.5 (2.7)
Verbal reasoning (years)	8.0 (0.0)
Numerical reasoning (years)	6.5 (1.6)
Visuomotor skills (years)	6.8 (0.4)
Social Intelligence (years)	7.1 (0.9)
VSMS	4.0 (2.4)
DQ	48.3 (17.7)
Gross motor skills (months)	21.1 (17.3)
Fine motor skills (months)	21.8 (1.3)
Adaptive (months)	21.3 (1.4)
Personal & social (months)	24.6 (1.4)

Table 3: Overall Cognitive gain during follow-up visits

Characteristic	Pre-surgical	First year	P value	Second year	P value	Third Year	P value
Mental age (months)	48.19(31.0)	54.7 (32.6)	0.003	58.8 (35.3)	0.0001	58.6 (38.3)	0.0001
IQ	67.0 (14.5)	66.7 (18.0)	0.86	67.6 (16.3)	0.61	67.2 (16.6)	0.67
Language	40.6 (28.2)	53.6 (32.3)	0.02	57.5 (34.8)	0.003	59.3 (36.4)	0.003
Mean memory	5.7 (1.5)	6.4 (2.4)	0.10	6.3 (2.0)	0.10	6.8 (2.3)	0.03
Non mean memory	5.7 (2.2)	6.0 (1.5)	0.78	6.5 (1.7)	0.35	6.5 (1.7)	0.35
Concept thinking	8.0 (1.7)	7.5 (2.6)	0.31	8.1 (2.3)	0.18	8.1 (2.3)	0.18
Non-verbal thinking	6.5 (2.7)	5.6 (1.2)	0.65	6.5 (2.5)	0.31	7.0 (2.3)	0.10
Numerical reasoning	6.5 (1.6)	6.7 (1.5)	0.59	7.7(3.0)	0.20	7.7 (3.1)	0.20
Visuomotor	6.8 (0.4)	6.5 (2.0)	0.78	7.0 (2.7)	0.25	7.0 (2.7)	0.25
Social intelligence	7.1 (0.9)	7.6 (2.0)	0.10	8.2 (2.1)	0.04	8.0 (2.0)	0.06
VSMS	4 (2.4)	4.6 (2.6)	0.004	5.1 (2.8)	0.001	5.3 (2.9)	0.001
DQ	48.3 (17.7)	46.6 (20.7)	0.89	47.0 (18.5)	0.91	49.5 (18.7)	0.46
Gross motor	21.1 (17.3)	24.5 (16.8)	0.17	26.2 (16.2)	0.04	27.0 (16.5)	0.04

Fine motor	21.8 (13.2)	24.3 (12.7)	0.21	28.3 (16.4)	0.02	28.3 (16.4)	0.02
Adaptive	21.3 (13.5)	25.2 (12.3)	0.07	28.3 (14.4)	0.01	29.1 (14.3)	0.01
Personal - social	24.6 (13.9)	28.1 (13.1)	0.10	30.3 (14.3)	0.06	31.8 (14.2)	0.01

The results of overall cognitive change of the entire group are shown in table 3. Comparing the results of the entire group, the mental age showed a steady increase after surgery which was of statistical significance ($p<0.05$) Fig 2. The overall mean mental age at the end of the third follow up was 58.6 ± 38.3 months. IQ showed a gradual gain on follow up but was not of statistical significance. Language had shown an upward trend irrespective of the side and etiology of the lesion which was of statistical significance. ($p=0.003$) The mean language score at the end of the third follow up was 59.3 ± 36.4 months as compared to the pre surgical status which was 40.6 ± 28.2 months. Meaningful memory was another domain which had shown a statistically significant difference as compared to the presurgical status but at the end of the third year [mean 6.8 ± 2.3, ($p=0.03$)]. The VSMS score also showed statistically significant increase after the surgery with a mean value of 5.3 ± 2.9 years ($p<0.001$). The mean gross motor, fine motor, adaptive and personal social skills at the end of the third follow up were 27.0 ± 16.5, 28.3 ± 16.4, 29.1 ± 14.3 and 31.8 ± 14.2 months respectively which were statistically significant.

Table 4: Cognitive status during the last follow-up visit (3rd) by etiological groups

Characteristic	RE	IHSS	SW	HM	Statistics df, F	P value
Mental age	76.6 (31.2)	30.8 (28.5)	47.1 (28.3)	22.7 (0.9)	3, 2.9	0.07
IQ	70.0 (15.8)		48.0 (0.0)		1, 1.6	0.24
Language	80.0 (31.7)	31.5 (31.8)	42.0 (27.4)	20.5 (7.7)	3, 3.4	0.04
Mean memory	7.2 (2.3)		5.5 (2.1)		1, 0.91	0.37
Non mean memory	6.5 (1.9)		6.0 (0.0)		1, 0.07	0.7
Concept thinking	9.0 (1.2)		4.0 (0.0)		1, 13.8	0.02
Non-verbal thinking	7.4 (2.5)		5.5 (0.7)		1, 1.06	0.33
Numerical reasoning	8.3 (3.3)		6.0 (1.4)		1, 0.82	0.39
Visuomotor	7.5 (2.9)		5.5 (2.1)		6, 0.75	0.42
Social intelligence	8.5 (1.9)		6.0 (1.4)		1, 3.0	0.12
VSMS	6.7 (2.6)	2.9 (2.6)	4.5 (3.0)	2.4 (0.6)	3, 2.3	0.12
DQ	50.0 (14.1)	45.8 (25.2)	71.0 (5.6)	31.5 (0.7)	3, 1.04	0.48
Gross motor	28.5 (10.6)	20.0 (18.3)	35.5 (34.6)	24.0 (0.0)	3. 2.4	0.2
Fine motor	27.0 (12.7)	36.0 (33.3)	28.5 (19.0) (0.0)	22.0 (2.8)	3, 0.21	0.88

Adaptive	33.0 (4.2)	32.5 (30.4)	30.0 (16.9)	21.0 (4.2)	3, 0.19	0.89
Personal - social	39.0 (4.2)	34.0 (28.2)	28.5 (19.0)	26.0 (5.6)	3, 0.22	0.87

Table 5: Cognitive status during the last follow-up visit (3rd) by etiological groups (Acquired Vs Congenital) excluding HM

Characteristic	Acquired (RE) N=9	Congenital (IHSS+SW) N=5	P value
Mental age	76.6 (31.2)	40.6 (26.1)	0.05
IQ	70.0 (15.8)	48.0 (0.0)	0.24
Language	80.0 (31.7)	37.8 (25.7)	0.02
Mean memory	7.2 (2.3)	5.5 (2.1)	0.3
Non mean memory	6.5 (1.9)	6.0 (0.0)	0.7
Conceptual thinking	9.0 (1.2)	4.0(0.0)	0.02
Non-verbal thinking	7.4 (2.5)	5.5 (0.7)	0.34
Numerical reasoning	8.3 (3.3)	6.0 (1.4)	0.39
Visuomotor	7.5 (2.9)	5.5 (2.1)	0.42
Social intelligence	8.5 (1.9)	6.0 (1.4)	0.12
VSMS	6.7 (2.6)	3.9 (2.6)	0.07
DQ	50.0 (14.1)	58.4 (20.8)	0.64
Gross motor	28.5 (10.6)	27.7 (24.3)	0.97

Fine motor	27.0 (12.7)	32.2 (22.8)	0.78
Adaptive	33.0 (4.2)	31.2 (20.1)	0.91
Personal - social	39.0 (4.2)	31.2 (19.9)	0.63

Cognitive outcome by etiology

Results of cognitive changes at the third follow up classified according to the etiology are shown in table 4. Significant differences between etiology groups were found using the one way ANOVA in the domains of language ($p=0.04$) and conceptual thinking ($p=0.02$). There was a significant change in language skills in patients with Rasmussen's encephalitis as compared to others. The mean language scores of patients with Rasmussen's encephalitis was the highest followed by Sturge – Weber disease, Infantile Hemiplegia and Hemimegalencephaly. Though patients with Rasmussen's encephalitis scored higher than the other with respect to most domains, they were not statistically significant. Table 5 grouped the patients into two categories 1) acquired which included only patients with RE ($n=9$) and 2) congenital which included patients with IHSS and SW ($n=5$). Patients with HM were excluded from this analysis because they have been proven to perform at poorer levels (53) as compared to the rest and that could skew the data. The results showed that patients with acquired pathology faired better in domains of mental age, language and conceptual thinking which were statistically significant.

Table 6 : Cognitive gain during the last follow-up visit (3rd) by side (all disease etiology)

Characteristic	Right	Left	Statistics U	P value
Mental age	59.0 (37.6)	58.2 (33.2)	31	0.95
IQ	70.0 (22.5)	64.5 (10.6)	7	0.88
Language	58.7 (42.0)	60.0 (32.8)	29	0.79
Mean memory	7.0 (2.1)	6.7 (2.8)	9.5	0.90
Non mean memory	6.2 (1.7)	6.7 (2.0)	6.5	0.68
Concept think	7.2 (2.3)	10.0 (0.0)	0	0.13
Non-verbal think	6.6 (1.3)	7.5 (3.4)	9.0	0.90
Numerical reasoning	7.0 (1.5)	9.0 (5.0)	5.5	0.57
Visuomotor	6.4 (2.5)	8.0 (3.4)	5	0.57
Social intelligence	8.4 (2.7)	7.5 (1.0)	8.5	0.73
VSMS	4.9 (2.8)	5.6 (3.2)	28.5	0.72
DQ	41.5 (22.3)	57.6(12.1)	4	0.34
Gross motor	28.7 (22.3)	25.2 (11.5)	8	1
Fine motor	24.5 (12.6)	32.2 (20.6)	7	0.8
Adaptive	23.7 (13.2)	34.5 (15.0)	4.5	0.34
Personal - social	27.0 (11.9)	36.7 (16.3)	4.5	0.34

Cognitive outcome by side of surgery

The results of cognitive changes of the entire sample at the third follow up with respect to side of surgery are shown in Table 6. No significant differences were seen in cognitive domains using the Mann- Whitney tests with respect to side in these patients.

Table 7: Cognitive gain during the last follow-up visit by side (Rasmussen's encephalitis)

Characteristic	RE Right (n=3)	RE Left (n=6)	Statistics U	P value
Mental age	96.6 (16.6)	66.5 (32.9)	5	0.3
IQ	77.3 (21.0)	64.5 (10.6)	3	0.4
Language	104.0 (6.9)	68.0 (32.7))	4	0.2
Mean memory	8.0 (1.7)	6.7 (2.8)	4.5	0.6
Non mean memory	6.3 (2.0)	6.7 (2.0)	5.5	0.85
Concept think	8.3 (1.1)	10.0 (0.0)	0	0.20
Non-verbal think	7.3 (1.1)	7.5 (3.4)	5.5	0.85
Numerical reasoning	7.6 (1.5)	9.0 (5.0)	4	1
Visuomotor	7.0(3.0)	8.0 (3.4)	3.5	0.7
Social intelligence	10.0 (2.0)	7.5 (1.0)	1.5	0.1
VSMS	7.2 (1.9)	6.5 (3.1)	7.5	0.7
DQ		50.0 (14.1)		
Gross motor		28.5 (10.6)		
Fine motor		27.0 (12.7)		
Adaptive		33.0 (4.2)		
Personal - social		39.0 (4.2)		

Results of cognitive changes of the group with Rasmussen's encephalitis (n=9, 56.25%) at the third follow up classified according to the side of surgery is shown in table 6. There were not enough patients to check out domains of gross motor, fine motor, adaptive and personal social skills with respect to the right side. 3 patients underwent right sided surgeries and 6 patients underwent left sided surgeries. No significant differences were seen in cognitive domains using the Mann- Whitney tests with respect to side in patients with Rasmussen's encephalitis. There were not enough patients with other etiologies to do the same categorisation.

Table 8: Cognitive gain during the last follow-up visit by gender (whole group)

Characteristic	Males	Females	Statistics U	P value
Mental age	54.8 (34.8)	54.6 (31.7)	29	0.95
IQ	66.5 (19.9)	67.7 (10.2)	10	0.76
Language	53.5 (34.9)	54 (30.8)	27.5	0.79
Mean memory	6.0 (2.5)	7.3 (2.5)	6	0.54
Non mean memory	6.0 (1.0)	6.0 (2.6)	7	0.71
Concept think	7.5 (2.6)			
Non-verbal think	5.8 (1.3)	5.3 (1.1)	7.5	0.71
Numerical reasoning	7.2 (1.3)	6.0 (2.0)	4.5	0.39
Visuomotor	7.0 (2.1)	5.0 (2.1)	3	0.57
Social intelligence	7.6 (2.4)	7.6 (1.5)	7.5	0.71
VSMS	4.7 (2.8)	4.6 (2.4)	28.5	0.87
DQ	34.0 (18.6)	54.0 (13.5)	2	0.22
Gross motor	20.0 (12.3)	18.6 (6.8)	4	0.62
Fine motor	16.5 (8.7)	29.0 (12.1)	3	0.4
Adaptive	17.5 (9.4)	30 (10.3)	2.5	0.22
Personal - social	21.0 (9.3)	33.0 (15.5)	3	0.4

Results of cognitive changes of the entire group with at the third follow up classified according to gender are shown in table 7. No significant differences were seen in cognitive domains using the Mann- Whitney tests with respect to gender in these.

Table 9: Predictors of gain in mental age of children at one-year follow-up

Variable[a,b]		β	SE	t	P value
	Sex	-.024	10.430	-.002	.998
	Etiology	-5.191	6.422	-.808	.440
	Side of surgery	-10.153	10.447	-.972	.356
	Age of onset of seizures	7.993	1.961	4.076	.003
	Seizure frequency	-.014	.015	-.943	.370
	Duration of seizure	6.018	1.851	3.251	.010

[a]= Dependent Variable: mental age at first year follow-up

[b]= Constant included in the variable

In the multiple linear regression analysis with the mental age at first year follow-up as the dependent variable the confounding effects of gender, diagnosis, side of surgery, age of onset of seizures, seizure frequency and duration of seizures were controlled. Despite controlling for the confounding effect, the mental age gain in these children post surgery was significant (F= 6.70; P=0.006). 69% of the variance for the outcome was explained by these variables (R^2=0.69). Age of onset of seizure and duration of seizure had a significant

influence on the mental age of the child at the first year follow-up (Table 9). Younger age and shorter duration of seizures prior to surgery showed positive mental age gains at follow up.

Table 10: Predictors of gain in social age of children at one-year follow-up

Variable[a,b]		B	Std. Error	t	P value
	sex	-.265	.638	-.415	.688
	Etiology	.031	.393	.079	.938
	Side of surgery	.599	.639	.936	.374
	Age of onset of seizures	.694	.120	5.785	.000
	Seizure frequency	-.002	.001	-1.805	.105
	Duration of seizures	.718	.113	6.333	.000

[a] = Dependent Variable: social age at first year follow-up

[b]= Constant included in the variable

In the multiple linear regression analysis with the social age at first year follow-up as the dependent variable the confounding effects of gender, diagnosis, side of surgery, age of onset of seizures, seizure frequency and duration of seizures were controlled. Despite controlling for the confounding effect, the social age gain in these children post surgery was significant (F= 12.43; P=0.001). 82% of the variance for the outcome was explained by these variables (R^2=0.82). Age of onset of seizure and duration of seizure had a significant

influence on the social age of the child at the first year follow-up (Table 10). Younger age and shorter duration of seizures prior to surgery showed positive social age gains at follow up.

Table 11: Changes in VSMS scores in relation with their pre op scores

% Impairment in pre op VSMS scores	N=16	No of patients who had gains in VSMS over three years (N=7)	No of patients who were static in VSMS over three years (N=9)	No of patients who had losses in VSMS over three years (N=0)
Gd 1(<25%)	3	2 (66.7%)	1 (33.3%)	-
Gd 2 (25-50%)	7	4 (57.1%)	3 (42.9%)	-
Gd 3 (50-75%)	4	1 (33.3%)	3 (66.7%)	-
Gd 4 (>75%)	2	0	2 (100%)	-

The children in this study were divided on the basis of their % impairment in VSMS scores into 4 groups as shown above. 7 out of 9 children had 25-50% impairment in their VSMS scores as compared to normal. Over the years after surgery, the maximum gains in VSMS scores were seen in patients with Gd 1 impairment followed by Gd2 and Gd 3. However, Gd4 patients remained static after surgery as opposed to deterioration over a period of time due to the natural history of the disease.

DISCUSSION

Studies assessing the effects on cognitive functioning of surgical and non-surgical candidates are of limited value, since these groups differ in variables like seizure frequency and distribution of epileptogenic tissue. Hence we designed a prospective single arm cohort study to report the effects of disconnective epilepsy surgery on cognition in a pediatric population which circumvents such difficulties by employing repeated assessments of the same patients during presurgical drug treatment and after surgery. This design also permits direct comparisons between groups on epilepsy-related variables. The cognitive tests were done to assess cognitive skills before and after surgery (annually) for a minimum period of 1 year and maximum of 3 years.

Seizure outcome:

Thompson and Duncan (55) proposed that periods of remission in a patient with intractable epilepsy have a protective role and at the least may result in an arrest of ongoing cognitive decline. They suggested that achieving complete seizure control, even after years of intractability, can have a beneficial impact on cognition as well as on psychological well-being and quality of life. Most published series quote a 75-80% chance of Engel's Class I outcome (53, 56, 57). But Devlin et al (58) highlighted the importance of the underlying pathology to the seizure outcome. 82.5% were seizure free post-operatively in those with IHSS. Pulsifer et al (59) had complete seizure freedom in 65% of their patients but patients with IHSS had 100% seizure freedom whereas Rasmussen's encephalitis and cortical dysplasia were 73% and 44% respectively. The overall decrease in seizure outcome may be

related to the fact that this group had 38% patients with cortical dysplasia which are known to be poor candidates for surgery. In our study, 15 children (93.75%) had Engel's Class I outcome or complete seizure freedom and 1 child had Class II (> 90% seizure reduction) outcome (Table 1). The child with Engel's Class II outcome was a patient with HM and operated at 4.75 years of age. Hence our findings also support the fact that patients with HM/ cortical dysplasia have a poor rate of seizure control as compared to IHSS and RE. (41) HM is a malformation of cortical development that includes large neurons and balloon cells in a dysplastic cortex with synaptic dysgenesis. Post surgery outcome is poor because contralateral abnormalities have been suspected in these so called normal hemispheres or it could be due to cumulative developmental delay from the very early onset severe seizure disorder (32, 33). The abnormalities may not be structural but may be functional in being epileptogenic. It is suggested that functional abnormalities are acquired very early in the non malformed hemisphere because of the diffusion of the epileptogenic process from the malformed to the nonmalformed hemisphere. This results initially in increasing the activity of the normal hemisphere which could be reversible till the end of the second year. During this period, the brain is still immature and undergoes maximum synaptogenesis and plasticity. Later on, the contralateral epileptogenesis which is present could become permanent. This also supports the recommendations to operate on these patients before the age of 2 years. Although the overall seizure free rate appears comparable between series, our results also highlight the relevance of underlying pathology to seizure outcome. Together with the review of other studies above, this suggests that the seizure free outcome from any study may be more influenced by the proportion of patients with RE and IHSS than by the proportions with other pathologies.

Overall Cognitive Outcome

Early studies found that that intellectual deterioration and loss of language following hemispherectomy were rare, and that surgery appeared to arrest the deterioration in cognitive function in some (60). The majority of patients in most reported series demonstrated no apparent change in cognitive performance after a median follow-up of 2-3 years (56, 57, 58, 59). Our results showed a steady gain in mental age after surgery which was statistically significant (p=0.0001) (Table 3). However, the mental age gain could also be a part of normal chronological development and hence cannot be commented upon as part of a cognitive domain. Devlin et al (58) found no apparent change in cognitive performance after a median follow up of 2.25 years. Similarly Freitag H and Tuxhorn I (21) found out that after 3 years of surgery, 75% performed at their pre operative level (gains of<15 and losses of<10 IQ/DQ points). They suggested that developmental gains may accumulate over a longer period and do not necessarily become evident in the early postoperative months. In our study, there was no apparent change in IQ/DQ at the end of the third follow up.

Our results showed that though DQ scores only showed a positive trend, the four domains of DQ assessment (gross motor, fine motor, adaptive and personal social skills) showed definite statistically significant gains in scores (p=0.04, 0.02, 0.01, 0.01) (Table 3). DQ is performed in children less than 6 years of age. Hence, a positive trend in the sub group domains may be pointing to the fact that surgery before 6 years of age may be more effective than after the age of 6. However, more data and studies are required to confirm this hypothesis. In the absence of seizures, the child's attention capacities increase and they benefit more from environmental input and engage more in social interaction. Parents are

likely to perceive this altered behaviour as developmental improvement, whereas improvement may become evident in a neuropsychological assessment only after a longer period (21, 54).

In our study, patients showed a statistically significant (p=0.03) increase in scores in domains of meaningful memory (Table 3) after the third year which points to the importance of a long term follow up in these patients. When these children are free of debilitating seizures, they should be subjected to cognitive rehabilitation and special schooling.

Our patients showed definite gains in VSMS scores in subsequent follow ups after surgery (p=0.001) (Table 3). This is an indicator of the adaptive skill of the child. Positive effects on quality of life during follow ups after surgical intervention are seen by reducing internalizing symptoms and increasing social interaction (34). An increase in adaptive skills would help the child to deal effectively with environmental stimuli and also improve on activities of daily living. Several studies indicate that quality of life measures paralleled the improvements in seizures control (36). This was in contrast to the results of Pulsifer et al (59) who showed no improvement but constant adaptive skills and Steinbok et al (56) who reported poor adaptive skills following surgery showing severe impairment in age appropriate activities of daily living.

Adult patients have shown to maintain stable levels of performance after drug treatment as well as following epilepsy surgery (28). However, follow up period is crucial to determine effects of cognition after epilepsy surgery. Smith ML, Elliot IM et al report little discernable change in cognitive function one year after pediatric epilepsy surgery (18). It should be long enough for reconfiguration of the individual, family functioning and for restitution at the level of brain plasticity to occur (54).

Etiology specific cognitive and language outcomes

The nature of the underlying brain disorder giving rise to the seizures appears to affect outcome far more than the procedure itself. When cognitive test scores were compared on the basis of etiology, our results showed a statistically significant improvement in the domains of language ($p=0.04$). Patients with RE scored the highest followed by SW, IHSS and HM (Table 4). The results were similar to that of Pulsifer et al (59) who also demonstrated that both patients with RE and IHSS score higher in general intelligence and receptive and expressive language than cortical dysplasia. But there was no appreciable difference between the RE and IHSS groups. In this study, on grouping them as acquired (RE) versus congenital diseases (IHSS + SW), patients with RE performed better than the congenital group (IHSS + SW) on domains of mental age, language and conceptual thinking which were statistically significant. The difference is seen in patients with Rasmussen's encephalitis because they indicate a halt in the ongoing cognitive decline (31, 39). The lack of obvious lateralization in infantile hemiplegia could reflect greater brain plasticity at the very early age at seizure (31, 39). Duchowny et al (61) suggested that developmental lesions and early-onset seizures do not displace language cortex from prenatally determined sites, whereas lesions acquired before the age of 5 years may cause language to relocate to the opposite hemisphere, but only when language cortex is destroyed. The period of rapid language development is between 2 and 5 years of age, with slower development continuing through puberty. Di rocco et al (53) suggests that, if brain damage occurs during this "critical" period, language functions could shift from one hemisphere to the other, with minimal consequences in terms of functional language skills. Language predetermined areas of the cortex are critical for language acquisition. If these prespecified areas for language

function are damaged, an impairment of language will result. Language, however, is thought to be lateralized since the age of six; so early brain damage affecting the dominant hemisphere usually may induce a contralateral function transfer. Evaluation of speech dominance is therefore important in determining the risk of an unacceptable postoperative deficit. The results of recent studies show that interhemispheric language reorganization is more likely to occur in patients with brain damage and epilepsy onset before 6 years of age; afterwards, there would be a reduction of capacity to transfer the language function to the right side. This is could probably explain why patients with RE in our study group did very well on tests of language as their mean age of seizure onset was also < 6 years. The capacity of language reorganization appears related to specific etiology: It is more frequent in destructive processes such as stroke and inflammation and less frequent in other pathologies such as developmental process and tumours (62).

This could explain the results of patients with acquired diseases performing better than patients with congenital diseases. In non lesional patients with epilepsy, the control of seizures allows language reorganization, suggesting a direct effect of epilepsy per se on linguistic organization. Unlike their adult counterparts, children with left hemisphere injury rarely suffer from long lasting aphasic symptoms (63)). Neuroimaging studies of children with focal damage to the left hemisphere indicate that such recovery or preservation of language functions may be associated with the recruitment of intact regions within the damaged left hemisphere, or of homotopic regions in the right hemisphere, or of both (64). This diversity of possible reorganization patterns makes it difficult to assess the role played by each hemisphere in language outcome when a focal injury has occurred. When, in contrast, the whole left cerebral hemisphere is completely disconnected and partially or completely removed, language functions can only be subserved by the lone right hemisphere.

Patients who have undergone hemispherectomy for the relief of intractable epilepsy therefore provide a unique model of brain reorganization for language functions during development Many studies point to reorganisation after a hemispherotomy. Ipsilateral representations were topographically different from contralateral representations, with ipsilateral representations occupying more anterior and lateral locations than contralateral representations in the healthy hemisphere (65).

Differences in postsurgical outcome between children with congenital and those with acquired cerebral damage have previously been observed in the domains of gross motor function (57, 58, 66). The gross motor function , overall functional skills and the degree of independence of activities of daily living post hemispherectomy was better in children with RE and IHSS than with cortical dysplasia/ HM. In our study too, patients with RE and IHSS performed better on tests of gross and fine motor skills (Table 4). The apparent lack of worsening of motor deficits in this group could be related to their early age at onset (with greater age-related plasticity) (31).

When cognitive outcomes were compared with respect to the side of surgery, there was no significant loss function following either right-sided or left-sided hemispherectomy in this study (Table 6) , which is also the reported experience of others (58, 60, 61). Also on comparing the RE group (Table 7), there was no difference in the performance between right or left hemispherotomy groups. This is in contrast to Pulsifer et al (59) whose right hemispherectomy RE patients scored significantly higher in receptive and expressive language than their counterparts who underwent left hemispherectomy. However, the number of patients enrolled in their study were definitely much higher (n=71) than most reported studies and hence considerable importance should be given to their observation.

Predictors of post operative cognitive outcome

Huttenlocher et al have noted that the majority (61%) of children with intractable epilepsy are developmentally challenged and that most of these children (73%) have their first seizure before 2 years of age. (67). These results suggest that young age of seizure onset is a risk factor for developmental retardation. This puts most of these children to have a low IQ/DQ to begin with before the surgery and the baseline pre op cognitive skills definitely predict the post operative outcome in these children (21).

In our results, when comparing the different variables, age of seizure onset and the duration of seizures prior to surgery had a significant influence on the mental and social age of the child at the first year follow-up. 69% of the variance for the mental age outcome and 82% of the variance for the social age outcome was explained by these variables (Tables 9, 10). Younger age and shorter duration of seizures prior to surgery showed positive mental age and social age gains at follow up. Onset of intractable epilepsy within the first 24 months of life is a significant risk factor for mental retardation, especially if seizures occur daily (20, 52) . It has been proved that when children with well controlled epilepsy are given a battery of tests including IQ tests, the age of onset is a major correlate of poor performance (20, 52).

Thomson and Duncan found no significant relation between cognitive change and age at onset, and thus did not support the hypothesis that early age at onset is a risk factor for decline (55). However, Freitag and Tuxhorn (21) proposed that duration of epilepsy was the only significant predictor of long term cognitive change: children with shorter intervals between onset of epilepsy and surgery had greater gains in DQ. Steinbok et al (56) also showed that with respect to cognitive and adaptive functioning, the most striking finding was the relationship of duration of epilepsy to cognitive skills, such that better outcome in terms of overall broad independence and functioning in all domains was associated with a shorter

duration of epilepsy. Also younger age at surgery was a positive factor with respect to aspects of postsurgical adaptive functioning, with higher scores related to earlier age at surgery.

Neuronal disruption sustained earlier in life has a more impairing effect on problem solving and psychometric abilities, than does brain damage that occurs after a longer period of normal growth and development (20). Thus the cognitive impairment in these children can be extrapolated as either because of a failure to develop normal cognition or loss of cognitive skills after they had developed normally for a while respectively. This finding supports the claim made by Devlin et al (58) that younger age at surgery maximizes the beneficial effects of surgery on future development, suggesting greater developmental plasticity early in life.

In this study (Table 11), we found an inverse relationship between grades of pre op impairment of VSMS scores to gains in VSMS scores on follow up. 66.7% of patients with grade 1 impairment showed gains in VSMS where as only 33.3% with grade 3 impairments showed gains in VSMS. All patients with grade 4 impairment remained static in scores on follow up. None showed any losses in VSMS scores on follow up. This further justifies the rationale for surgery in these patients with surgically remediable epilepsy irrespective of their pre operative cognition. A halt in the cognitive decline or a gain in cognition score is acceptable across all grades of pre operative impairment as opposed to a steady deterioration along the natural course of these diseases.

Strengths of the study:

Not withstanding the limitations that will be discussed below this study has the following strengths. This study had an *a priori* sample size calculation with a power of 90% to detect differences in the cognitive changes. Measures that are universally standard and

those that were sensitive to changes in cognition over time were used in this study. The cognitive assessments were done by a qualified and experienced rehabilitation psychologist. The cognitive assessment was done independently from the team that carried out the surgical procedures. A single rater was used to decrease the inter-rater reliability issues. The attrition was overcome by the widely used technique of intention-to treat analysis. Confounders for the outcome of mental age and adaptive behaviour were controlled with multiple regressions.

Limitations of the study

The main caveats in this study are that two children had undergone cognitive training post surgically and this could have inflated the cognitive gains in this small sample size. Secondly, sampling was purposive in nature. Finally, presurgical and post surgical cognitive assessment if had been done by different psychologists, with a good inter-rater reliability, would have reduced the rater bias further.

Conclusions

Seizures that are not controlled in children adversely influence the development of cognitive functions during the period of brain plasticity. In our experience, over 90% of children sub hemispheric and hemispheric epilepsy syndromes achieve an excellent seizure outcome following surgery. In the series, there was a significant gain in the mental age, language, meaningful memory and social age (adaptive behaviour) in the immediate postsurgical period. These gains also continued into the second and third years of follow-up as well. Patients with RE or acquired diseases perform better on tests of cognition as compared to congenital diseases (IHSS/ SW/ HM). There is no definite relation between cognitive outcome with respect to the side of hemispherotomy. Following seizure freedom,

development of functions in the residual brain occur and, this in turn leads to a "catch up" of adaptive functions. The IQ/DQ might not change significantly after surgery but mental age, language, social intelligence, gross motor, personal and adaptive skills show definitive gains. Age of seizure onset and duration of seizures prior to surgery are independent variables which predict the post operative mental and social age. These developmental gains may accumulate over a longer period and do not necessarily become evident in the early postoperative months. Early diagnosis of intractability and investigations directed towards the identification of surgically remediable epilepsy syndromes prior to the cessation of neural plasticity should be the cornerstone of management of pediatric epilepsy.

Future trends:

This study focussed on the general cognitive abilities of the children with intractable epilepsy who have undergone hemispheric epilepsy surgery. Future studies should document changes in specific areas of cognition like language, memory, attention and other executive functions of the brain. Also, a study design with larger numbers of patients and improved sampling technique like a random sampling, as well as better blinding to improve the rater bias could be incorporated in the future study designs.

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Appendix 1 (Pre operative Proforma)

- Name, age, sex, hospital no, address and telephone, email
- Age of seizure onset
- Types of seizure at onset
- Types of seizure at present
- Seizure frequency per week
- Duration of epilepsy
- Duration of loss of schooling
- Duration of motor deficits
- AED's administered and dose
    1.
    2.
    3.
    4.
- Age at surgery
- Type of surgery
- Visual fields
- EEG data

Ipsilateral

Contralateral

- Previous surgery
- MRI – side of lesion and its details
- Etiology of the condition
- Histopathology

Appendix 2

Informed Consent

Patient's Name :

Hospital Number:

The procedures and investigations required for the study "Cognitive changes after surgery in intractable hemispheric/subhemispheric epilepsy." have been fully explained to me in a language I understand. I have no objection to enrol my ward in this study, or for the use or publication of the data collected for any scientific or academic purpose.

Signature of the guardian

Relationship to the patient

Date:

Address

Witness

Appendix 3 (Data Sheet)

Fig 1: Flow chart for management of epilepsy

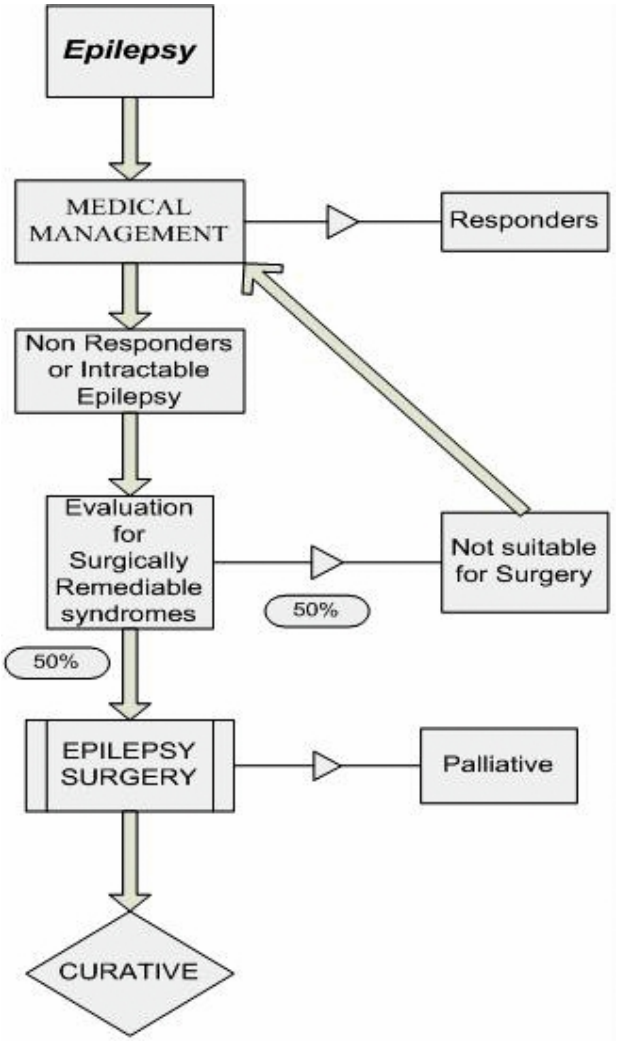


Fig 2: T2W Axial flair MRI image of a patient with infantile hemiplegia seizure syndrome

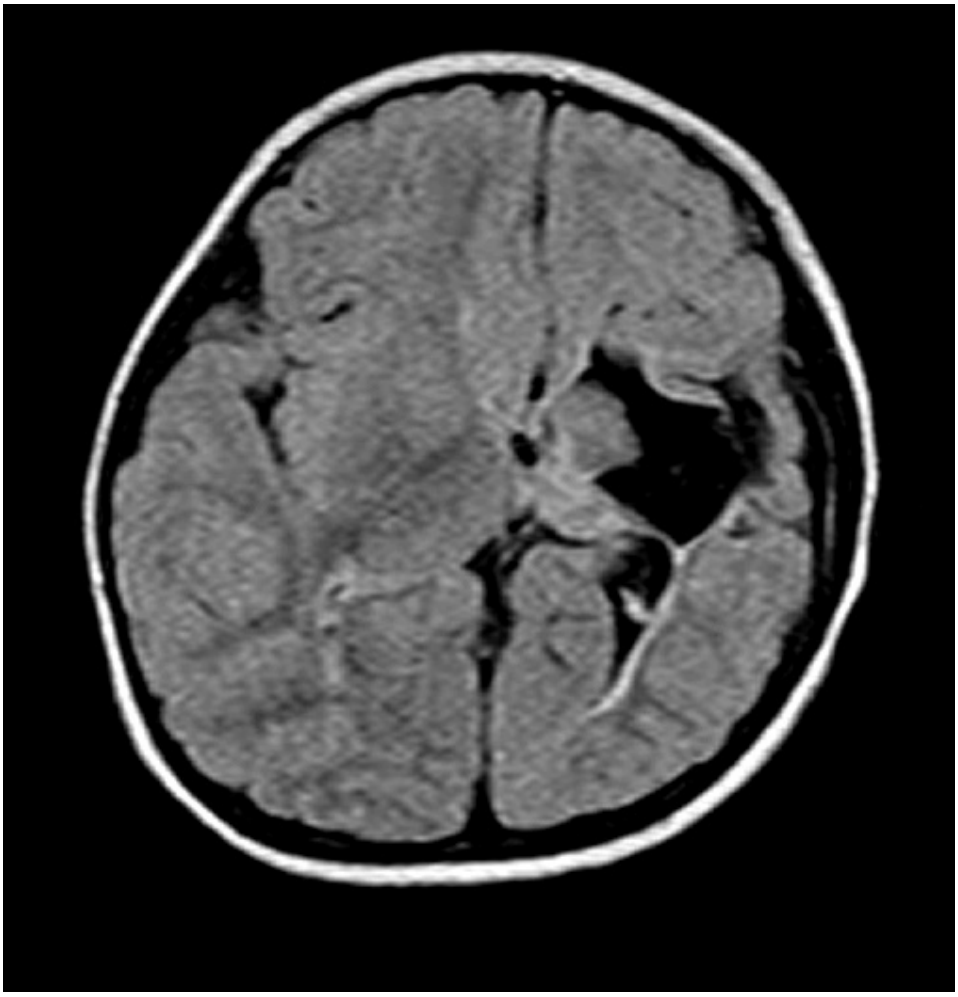


Fig 3: T2W Axial flair MRI images of a patient with Rasmussen's encephlitis taken six months apart (A) and (B) showing progression of disease

A **B**

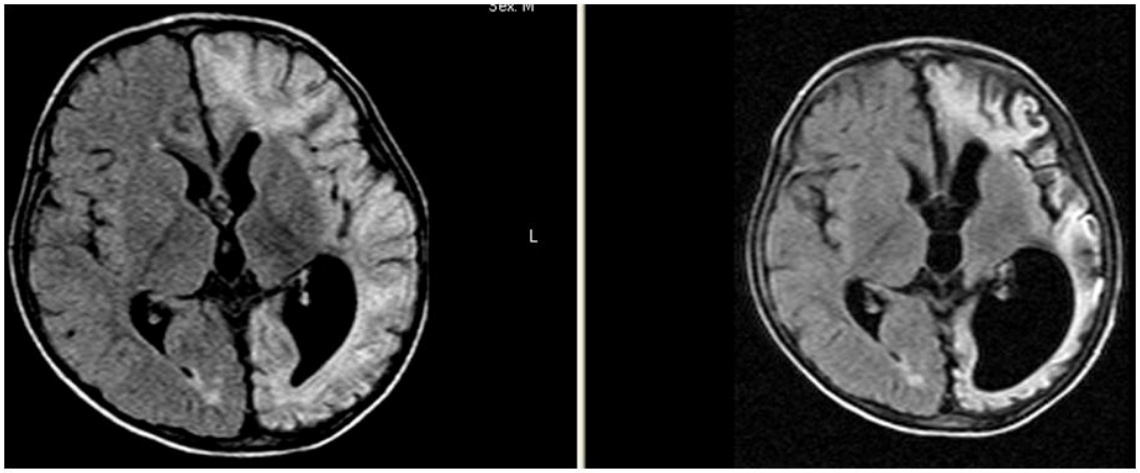


Fig 4: Intraoperative photograph of the abnormal hemisphere in a patient with Rasmussen's encephlitis

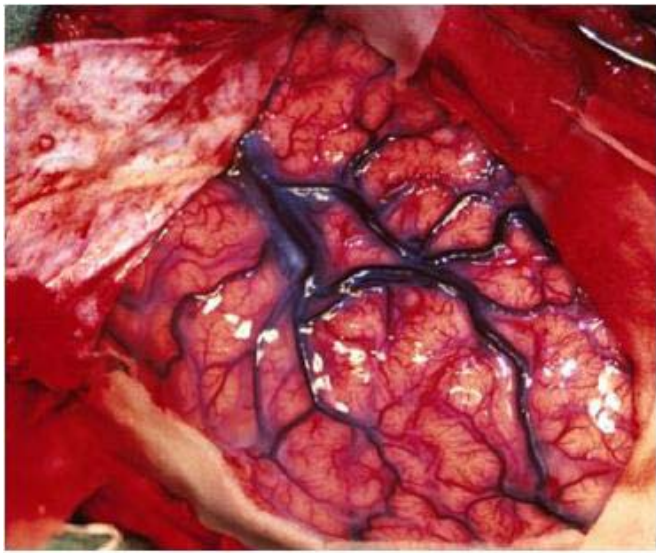


Fig 5: T1W Axial gadolinium MRI image (A) of a patient with Sturge Weber disease showing left hemispheric leptomeningeal angiomatosis (B) Intraoperative photograph

A **B**

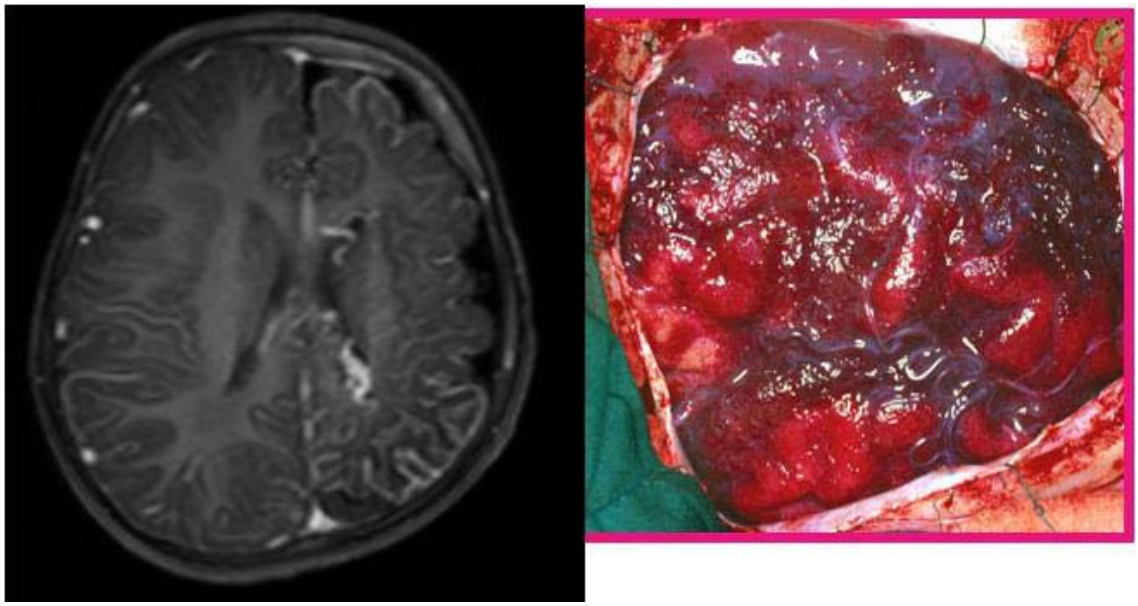


Fig 6: T2W Axial Flair MRI Image (A) of a patient with right hemimegalencephaly showing an enlarged right hemisphere with thickened cortical mantle, distorted ventricular anatomy and widened gyri (B) Intraoperative photograph

A **B**

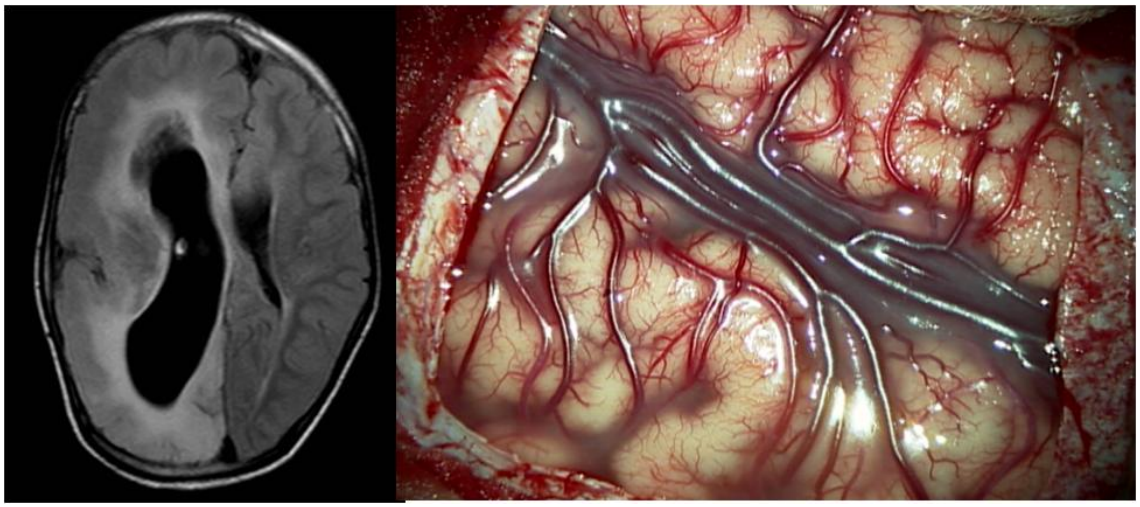


Fig 7: Intraoperative photograph of peri-insular hemispherotomy showing the supra and infrainsular windows

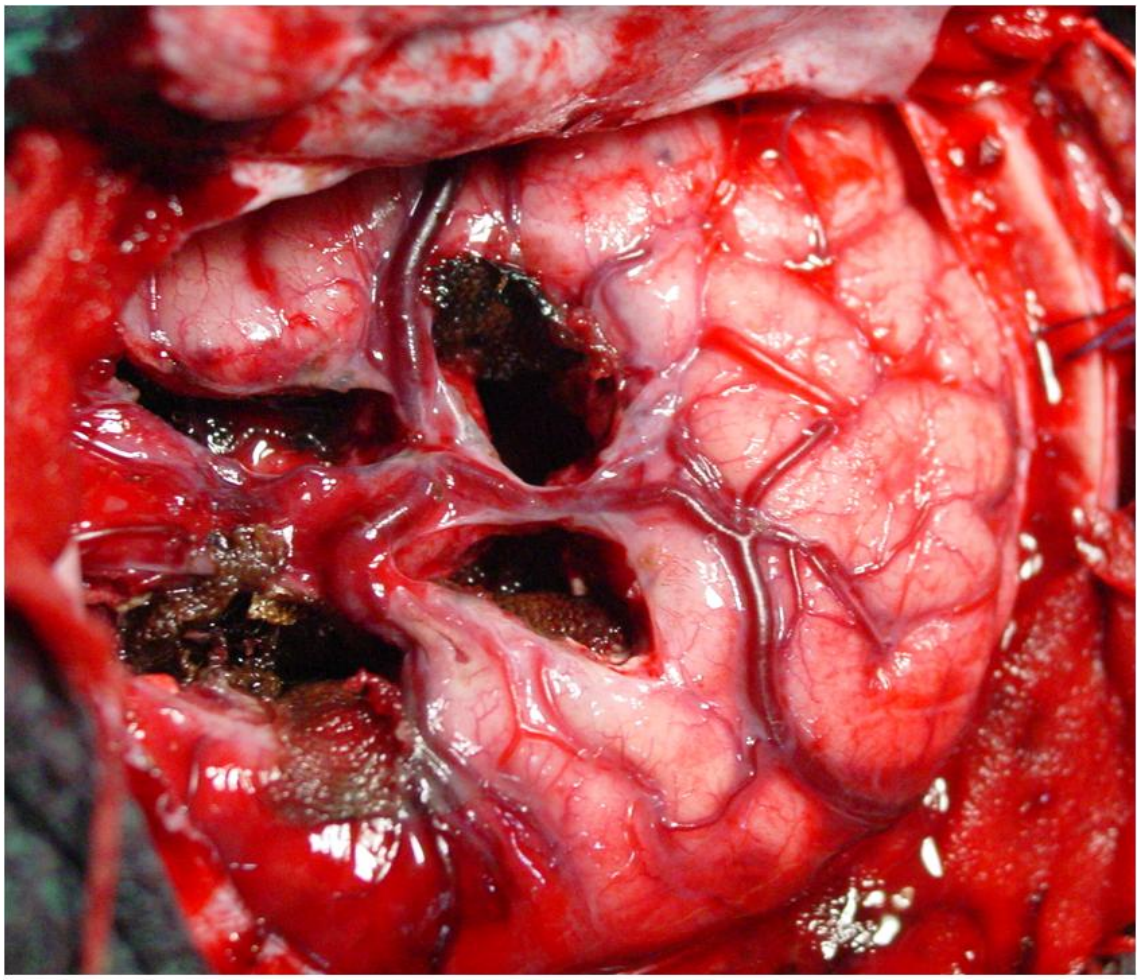


Fig 8: T2W Axial Flair (A) and T1W Sagittal Flair (B) images showing a right temporo-parieto occipital atrophic lesion resulting in a porencephalic cyst leading to subhemispheric epilepsy

A **B**

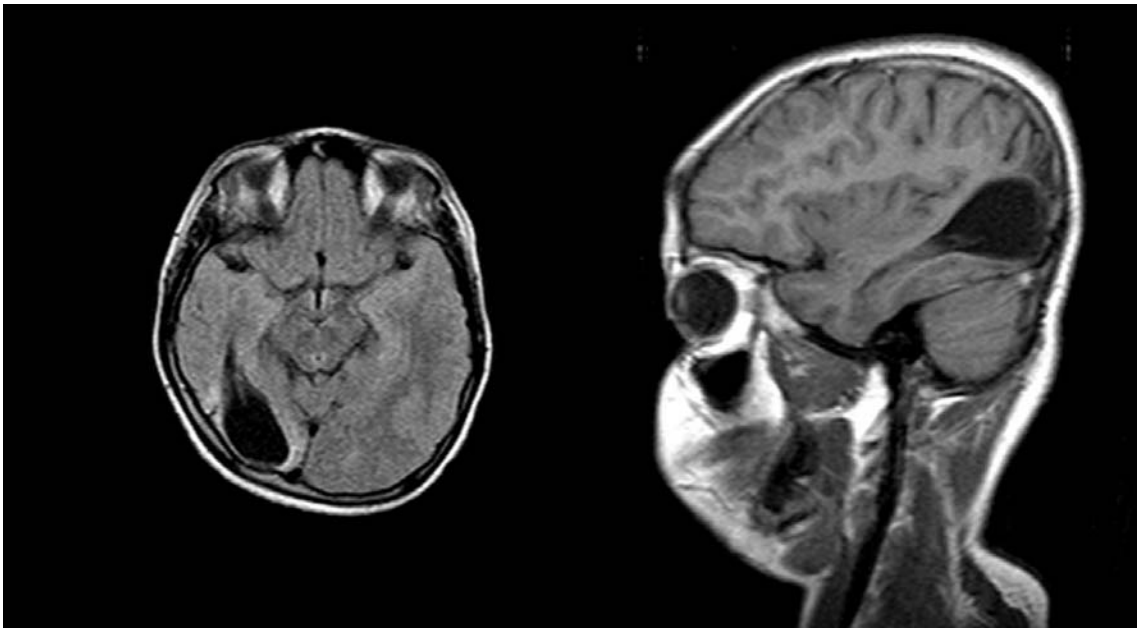


Fig 9: (A) Anatomical model of a peri-insular posterior quadrantectomy

(B)Intraoperative photograph of the same

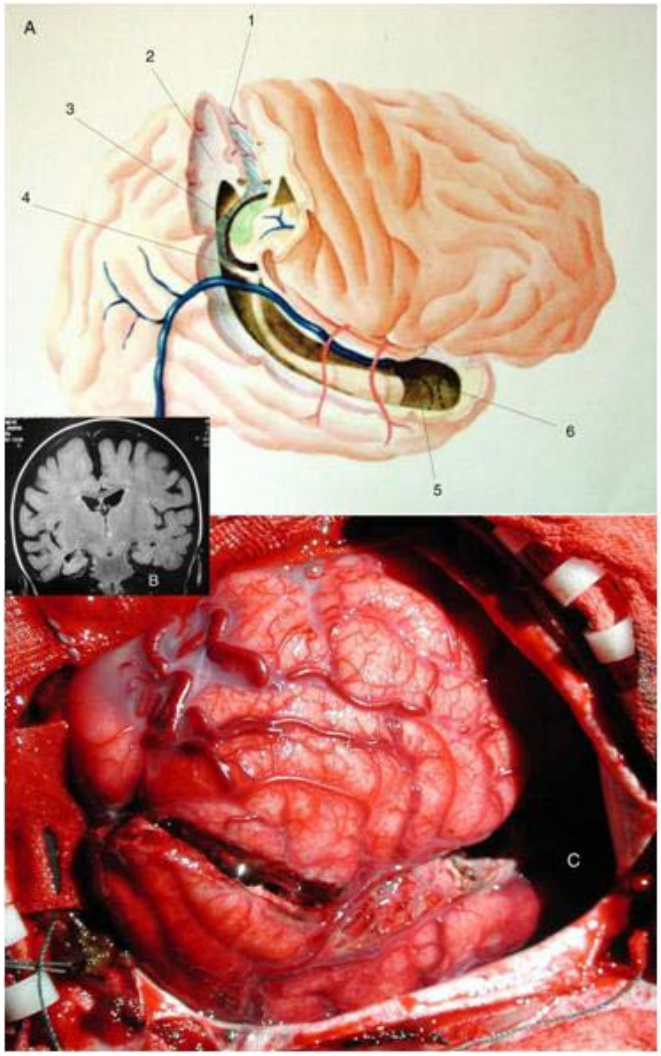
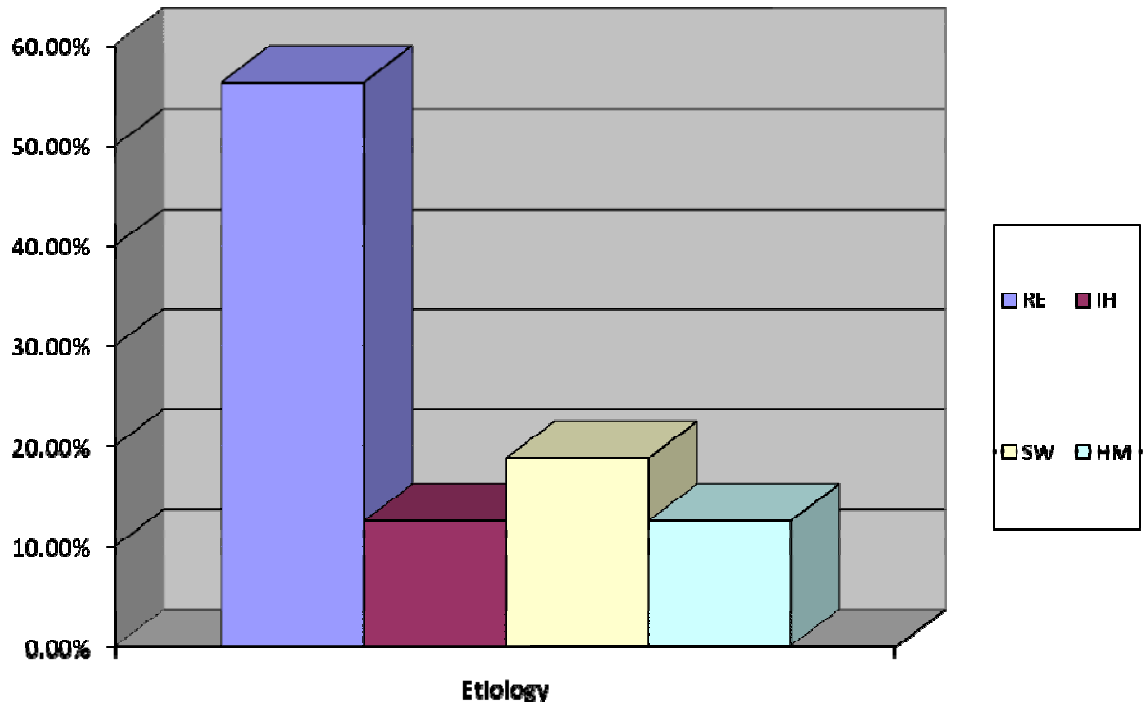


Fig 10: Etiology of Epilepsy



RE – Rasmussen's encephalitis (n=9 , 56.25%)

SW - Sturge weber syndrome (n=3, 18.75%).

IH- Infantile hemiplegia seizure syndrome (n=2 , 12.5%)

HM- Hemimegalencephaly (n=2 , 12.5%)

Fig 11: Mental age trends of the sample

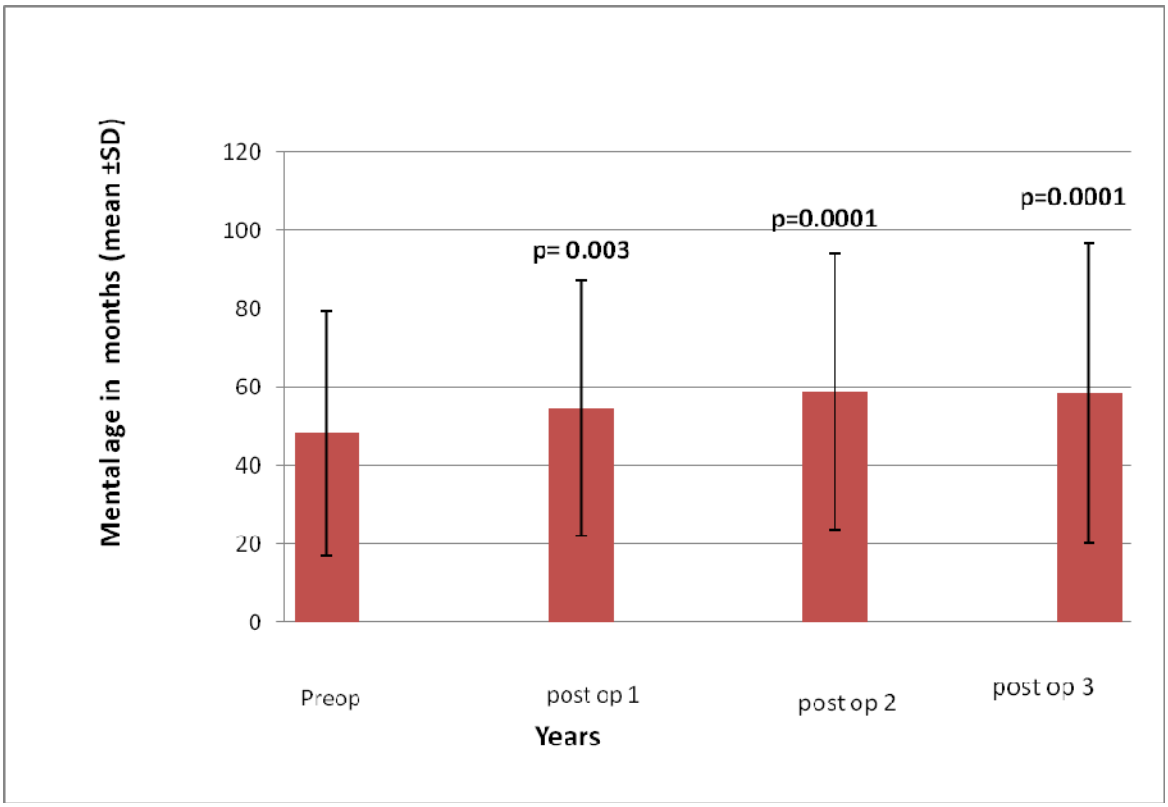


Fig 12: Language trends of the sample