MRI spectrum of cerebral palsy in correlation with clinical profile

A dissertation submitted in partial fulfillment of MD Radiodiagnosis

(Branch VIII) examination of the Tamil Nadu Dr. M.G.R Medical

University, Chennai to be held in April 2014

CERTIFICATE

This is to certify that the dissertation entitled "MRI spectrum of cerebral palsy in correlation with clinical profile" is the bonafide original work of Dr. S. Timothy Chelliah submitted in partial fulfillment of the requirement for MD Radiodiagnosis (Branch VIII) Degree Examination of The Tamil Nadu Dr M G R Medical University, Guindy, Chennai to be held in April 2014.

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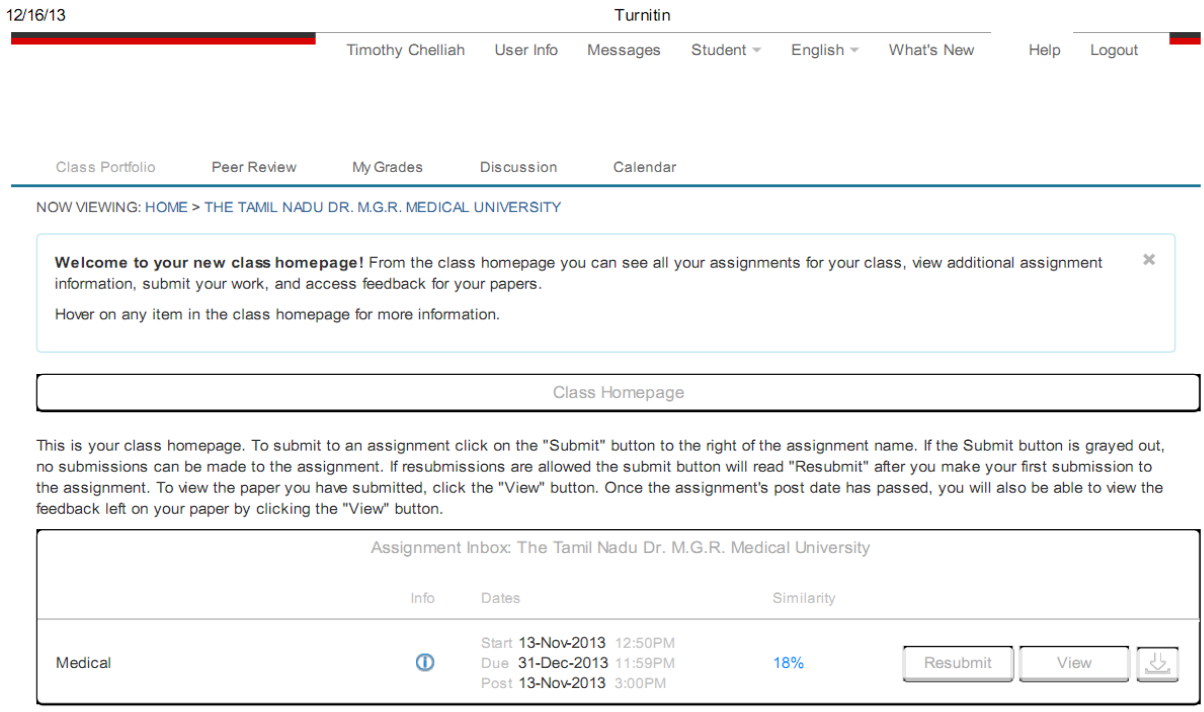
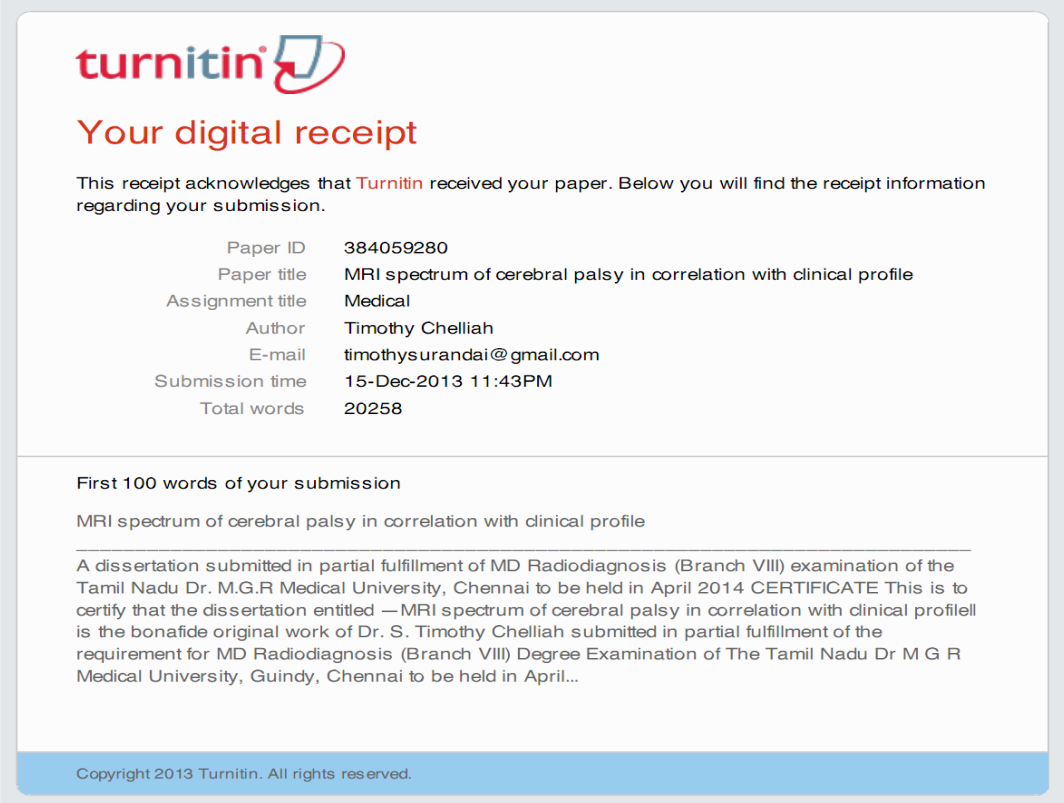
PLAGIARISM CERTIFICATE





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Spectrum of MRI features of cerebral palsy with relation to the clinical profile.
Dr. S. Timothy Chelliah, PG Registrar, Radiology, Dr. Sridhar Gibikote,
Dr. Sunithi Mani, Radiology, Dr. Samuel P Oommen, Developmental Pediatrics Unit.

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2. Agreement

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Contents:

INTRODUCTION:

Cerebral palsy (CP) is defined as a group of persistent non-progressive disorder of movement and posture that can be attributed to injury of the developing fetal or infant brain and manifests itself before three years of age (1). About 35% to 50% of all children with cerebral palsy will have an accompanying seizure disorder, some degree of mental retardation, learning disabilities, impaired vision, speech, hearing, or language problems (2).

Cerebral palsy poses considerable diagnostic and therapeutic challenges to the pediatrician, neurologist and orthopedic surgeon. The degree of involvement ranges from mild with minimal disability to severe wherein it is associated with severe co-morbid conditions. It is one of the three most common lifelong developmental disabilities producing significant burden to the affected individuals, parents and their families. Autism and mental retardation are the other two conditions (3).

Literature available till date widely reports the incidence of structural abnormal MRI brain findings in cerebral palsy children ranging from 70-100% of cases (4–7). Many studies have also shown that many progressive conditions like slowly progressive leukodystrophies can mimic clinical features of Cerebral Palsy, as the former can be potentially treated thereby slowing or arresting disease progression; hence MRI brain is part of the diagnostic protocol in all children with clinical diagnosis of Cerebral Palsy.

To date many studies have been done evaluating the spectrum of MRI findings in children with cerebral palsy across the globe. However, in the Indian scenario, there are but a few studies addressing the issue of MRI findings. Those reported in literatures are ones wherein

the number of patients are restricted to a small subset of patients (8). This however does not reflect the prevalence of cerebral palsy in India which is 2 per 1000 live births.

This study describes the diverse spectrum of neuroimaging features on MRI brain in children with Cerebral Palsy (CP) between the ages of 1year and 16 years who were evaluated at the Developmental Pediatrics and Pediatric Neurology Units, Christian Medical College Hospital, Vellore and then referred to Department of Radiodiagnosis for MRI of Brain during the period March 2012 to October 2013.

RATIONALE BEHIND THE STUDY:

The spectrum of MR imaging findings has been widely described in children with cerebral palsy (CP). However, most of the correlative studies have been done in developed countries and there is very little data from India. This study is done to address the paucity of data regarding the MRI features of CP in Indian children and to understand the prognosis of children with CP.

There is a need to understand the proportion of different clinical subgroups (topography), gestational age groups (term or preterm) and different peculiar perinatal history of developing countries like neonatal hyperbilirubinemia and compare them with the MRI findings. These results need to be compared with the results reported in the developed countries.

The pathological basis of cerebral palsy can be better appreciated by evaluating the imaging findings on MRI. Advanced neuroimaging has no doubt added new horizons to the conceptual understanding of cerebral palsy not only by the clinicians, but also has enabled the parents to comprehend the nature and extent of their child's neuro-morphological condition. Imaging in correlation with the clinical spectrum of findings is expected to aid in predicting the outcome and plan for rehabilitation.

There is paucity of data regarding involvement of corpus callosum in CP children. Studies regarding corpus callosal measurements have been done in smaller number of CP patients who had only one clinical subgroup, till date (10).

AIM:

To describe the spectrum of imaging features on MRI brain in a group of Indian children with clinical diagnosis of Cerebral Palsy (CP).

OBJECTIVES:

i. (a) To correlate the MRI features of CP with perinatal history, clinical features and topography (clinical subgroups).

(b) To assess whether imaging adds value in patient management and counselling.

ii. To correlate the involvement (thinning) of the corpus callosum (CC) with clinical subgroups (topographical patterns) of CP and periventricular leukomalacia (PVL) grades.

LITERATURE REVIEW:

History of cerebral palsy:

The history of cerebral palsy dates back to ancient Egypt, archeological surveys revealed two ancient drawings dating back to 5th century BC depicting individuals, who later were diagnosed to have spastic cerebral palsy. William John Little was one among the pioneers who described the clinical findings of cerebral palsy in 1843 in his seminal work "Deformities of the Human Frame", hence the name "Little's disease" for spastic diplegia of CP. The term "Cerebral Palsy" per se was coined by the British physician Sir William Osler in 1889. Sigmund Freud classified CP into three groups based on causes like maternal, perinatal and postnatal causes. However by 1947 the American academy of cerebral palsy was formed, it was another decade before the exact definition of cerebral palsy was formed in 1957 by the Little's club with a classification into 6 topographical types. Series of redefinitions were done subsequently in 1960, 1980, 1987-1990 and 1998 owing to greater understanding of the disease etiology and manifestations (11).

Cerebral Palsy in India:

Cerebral palsy is by far the most common cause of chronic childhood disability in India. Pioneering work in India was done at Children's Orthopedic Hospital, Mumbai by a team led by the visionary Dr. Perin Kavas Mullaferoze in late 1950's. The Indian Academy of Cerebral Palsy formed by doctors, rehabilitation professionals, parents and people engaged in prevention and management of CP celebrate, October 3rd the 'National Cerebral Palsy Day' since 2010 (12,13).

Definition:

Cerebral palsy was defined as a group of non-progressive permanent disorder of movement and posture that can occur after damage to the developing fetal or infant brain (1). This definition of cerebral palsy was annotated by Bax in 1964. According to the International Workshop on Definition and Classification of CP was held in Bethesda, Maryland, July 11 to 13, 2004, the current definition states that "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, by epilepsy and by secondary musculoskeletal problems." Thus the definition of cerebral palsy has four main components:

(a) CP is a disorder of movement and posture;

(b) It results from an abnormality in the brain;

(c) It is acquired early in life; and

(d) the condition is static at the time of recognition (11,14)

Added to the varied manifestations of cerebral palsy, secondary conditions caused by the motor impairment compound the clinical scenario and impede the therapy, these factors to mention a few and others like varied degree of mental retardation, improper speech and communication skills are other factors which contribute to the child's impairment. No two children with cerebral palsy are the same, varying degrees of impairment compound the therapeutic approach, hence every child requires to be approached individually and therapeutic approach pertaining to rehabilitation is thereby unique.

Classification is important in understanding the individual child's impairment, and for

coordinating management of Cerebral Palsy. A multidisciplinary approach to management of CP has left to varied classifications based on the vantage point of the care giver. For e.g: An orthopedic surgeon requires a definition of the limbs affected and the extent of impairment in order to direct treatment, whereas neurosurgeons and radiologists approach the disease from the causative point of view of the brain abnormality and descriptors for imposing white and gray matter in an effort to determine the type of brain injury or brain malformation, that would aid in predicting the extent and severity of cerebral palsy.

Topographical distribution of the impairment further defined by plegia or paresis is required by the pediatricians and the physiotherapists. Parents of the affected child, occupational therapists and school administrators would concern themselves with the severity of the disease. This would help them to plan the benefit programs and educational resources directed to the child.

These multiple approaches to viewing a single disease, a move to evolve a universally accepted classification system has led to the evolution of the Gross Motor Function Classification System (GMFCS) (15), to increase consistency and expand the ability to trend prevalence, life expectancy, societal impact, and prevention measures.

Classification based on severity:

1. Mild – These children who can move without assistance with no limitations of the daily activities.

2. Moderate – These children require orthopedic braces, medications & adaptive technology to aid them in daily activities.

3. Severe – These children are confined to a wheelchair and will have significant challenges in accomplishing daily activities.

Classification based on topography:

Cerebral Palsy is topographically classified as is monoplegia, hemiplegia, diplegia, triplegia and quadriplegia. Triplegia and monoplegia are relatively uncommon. In fact, there is significant overlap of the affected areas; in such clinical scenarios the terminology mixed cerebral palsy has been used (3). The prefixes are based on topography, the post fix has two components, plegia for paralysis and paresis for weakness, based on the severity of involvement.

Monoplegia – Monoplegic CP has isolated upper or lower extremity involvement. This has a mild clinical presentation, and carries a favorable prognosis, however this type is rare.

Hemiplegia – This is a unilateral paresis with upper limbs more severely affected than the lower limbs. Hemiplegic CP is seen in 17% of preterm infants and 56% of term infants. Pathogenesis is multifactorial. Hemiplegic CP impairs voluntary movements, predominantly the hand functions, in these children pincer grasp of the thumb, extension of the wrist and supination of the forearm are the most common hand functions affected. In the leg, dorsiflexion and aversion of the foot are commonly impaired. The flexor tone is increased with hemiparetic posture. There is flexion deformity at the elbow. Palmar grasp can persist for many years. Affected limbs may show sensory abnormalities. Stereognosis, two point discrimination and position sense are also defective. Seizures can occur in more than 50% of hemiplegic CP children. Cranial nerve abnormalities most commonly facial nerve palsies, visual field defects and homonymous hemianopia are also can be seen (3).

Diplegia - This is associated with prematurity and low birth weight. Almost all preterm infants with spastic diplegia on neuroimaging exhibit cystic periventricular leukomalacia. The most common ischemic brain injury in premature infants is Periventricular Leukomalacia (PVL). The border zone or watershed zone at the end of arterial vascular distributions and the white

matter adjacent to the lateral ventricles are affected by ischemia (3).

Triplegia – Spastic triplegia involves three extremities. It usually involves both lower extremity and one upper extremity. The spasticity results in involved limbs causes mild coordination defects in the uninvolved limb. UMN signs results with characteristic scissoring and toe walking (16).

Paraplegia – Only lower limbs are affected. The spasticity results in gait disturbances. This may masquerade as hereditary spastic paraplegia.

Quadriplegia –It is the most severe form of CP involving all four limbs. Trunk and upper limbs are more severely affected than the lower limbs. It is due to severe acute intrapartum hypoxia. Neuroimaging shows extensive cystic degeneration of the brain-polycystic encephalomalacia, polyporencephalon, polymicrogyria and schizencephaly. Few voluntary movements, vasomotor changes of extremities are common. These children present with peudobulbar signs, recurrent aspiration of food material, and difficulty in swallowing (referred to as pentaplegia) (3).

Classification based on neuromuscular deficit:

Cerebral palsy classification further depend upon the nature of neuromuscular deficits like (i) spastic (ii) hypotonic (iii) dyskinetic which includes dystonic and choreoathetoid (iv) ataxic and (v) mixed. Out of these types spastic cerebral palsy is the commonest and accounts for approximately 75 % of all the cases.

1) Spastic CP (Pyramidal): Pyramidal involvement with upper motor neuron signs (UMN), weakness, hypertonia, hyperreflexia, clonus and positive Babinski seen in spastic type of cerebral palsy. Contractures are common in spastic type of cerebral palsies (3).

2) Dyskinetic CP (Extrapyramidal): Dyskinetic CP mainly characterized by extrapyramidal involvement and movement patterns secondary to abnormal regulation of tone, defects in postural control and coordination deficits. The important clinical features are chorea, rigidity, choreoathetosis, athetosis dystona and ataxia. This can also be seen in post asphyxiated children who develop cerebral palsy. Body position, emotional state and sleep determine the severity of the dystonic posture. Primitive reflexes are more prominent in dyskinetic CP which persists for a longer time. During sleep there is significant decrease in the tone of affected limbs with elimination of movement patterns. Severely affected children may have persistent hypotonia. Posture control and coordination abnormalities are noted. There is no cognitive impairment in the majority of dyskinetic CP. Contractures are uncommon in this type of CP. It has been proven that high incidence of sensorineural hearing loss with this type of CP (3,16).

3) Mixed: Mixed pattern of involvement is seen in 30% of cerebral palsy children (3).

Gross Motor Function Classification System

This classification system is used for research purposes and was formulated to attain a uniformity of the classifications (15). It is by far the most comprehensive classification system used in CP and has been revised in 2007 (GMFCS-E&R) which is redefined under the umbrella of age groups before 2^{nd} birthday, 2^{nd} – 4^{th} birthday; 4^{th} – 6^{th} birthday; 6^{th} – 12^{th} birthday & 12^{th} – 18^{th} birthday. An overview of the classification is enlisted below; detailed classification is out of scope.

LEVEL I - Walks without Limitations

LEVEL II - Walks with Limitations

LEVEL III - Walks Using a Hand-Held Mobility Device

LEVEL IV - Self-Mobility with Limitations; May Use Powered Mobility

LEVEL V - Transported in a Manual Wheelchair.

INCIDENCE AND PREVALENCE (EPIDEMIOLOGY):

Cerebral palsy occurs in 0.2% of live births, but infants born before 28 weeks of gestation have a 50 fold elevated risk when compared with infants born at term, with prevalence 1.4-3.6 per 1000 (15) between 6% and 26% (1,17–19). Data from a few Indian resources show that the prevalence may be 1.5 to 2.5 per 1000 live births (20) and 3.3-10.3 per 1000 live births (21). However the exact data regarding the incidence, prevalence and clinico-radiological spectrum of CP in India remains unclear, in spite of reports stating the prevalence in India has remained steady over the last 20years (19, 22).

Advances in perinatal care, refined appropriate neonatal management techniques and advent of mechanical ventilation to neonatal intensive care have led to a gradual increase in the number of preterm born survivors which has led to increase in the prevalence of preterm born cerebral palsy children (9,22). Recent times wherein significant strides have been made in terms of Reproductive Child Health care has led to a steady decline in infant mortality rate; this probably is another factor which has led to an actual increase in the incidence and severity of CP owing to perinatal risk factors (3). The recent systematic review and meta-analysis conducted and reported wherein a total of 49 population-based studies were selected, based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses), stated that the overall prevalence of cerebral palsy has remained constant in recent years (23).

The summary of the study states that the prevalence of CP as follows:

- The pooled overall prevalence - 2.11 per 1000 live births.

- Prevalence stratified by birth weight group: Children weighing 1000 to 1499g at birth - 59.18 per 1000 live births, however there was no significant difference on pair wise meta-regression with children weighing less than 1000g.
- Prevalence of CP by gestational age was highest in children born before 28 weeks' gestation (111.80 per 1000 live births)

ETIOPATHOGENESIS OF CEREBRAL PALSY:

Literatures available from across the globe have evaluated children with cerebral palsy. In the European Cerebral Palsy Study done by Bax et al. there were 45.5% of children born at preterm (6). Another study by Robinson et al. at Royal Children's Hospital in Melbourne, Australia included 34 % of preterm born children. Victorian Cerebral Palsy Register showed that 38% of 1500 children with cerebral palsy between 1990 and 2002 were born preterm (7).

To our present knowledge there are a few studies done in Indian population. To name a few, one is by Prasad et al. at department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, where they have evaluated 102 children with cerebral palsy (8) and found the group contained only 17.6% of preterm born cerebral palsy children. Another study done by Singhi et al. at department of Paediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh, India showed that out of 1000 children evaluated at the rehabilitation centre for disabled children, Chandigarh from 1985 to 1993 only 13.2% were born preterm (9).

This is in stark contrast to the western scenario, wherein preterm births dominated the cause of cerebral palsy compared to Indian children. In other words we can conclude that term birth asphyxia is still the most common cause of cerebral palsy in Indian children contrary to the

children in developed countries. The study done at Chandigarh also enlisted other important causes of cerebral palsy in Indian scenario such as low birth weight, neonatal jaundice and neonatal sepsis which contributed to 56.4% of the 1000 cerebral palsy children from rehabilitation centre for disabled children, Chandigarh (9).

Summing up, the leading causes of CP in developing countries like India are term birth asphyxia, neonatal sepsis, bilirubin encephalopathy and low birth weight which is in contrast to the developed countries wherein prematurity accounts for a significant percentage of etiological causes of CP, the remainder would be term born children as seen globally. The significant percentage due to prematurity in developed countries is due to excellent neonatal intensive care leading to higher survival rates (22).

Terminology description for the etiological factors:

(a) Birth asphyxia:

For the accurate labeling of birth asphyxia one has to consider the APGAR score. But it may be difficult to get the APGAR score when the cerebral palsy child from developing countries like India has been evaluated in developmental pediatrics department. Persisting large proportion of home deliveries by untrained people, illiterate parents and loss of neonatal health data in our country are the few causes of difficulty in getting the exact APGAR score. So in the absence of APGAR score the following criteria are used: (i) meconium-stained amniotic fluid, (ii) history of delay in the initiation of cry more than 5 minutes after birth, (iii) baby turned blue immediately after delivery and requires oxygen therapy, (iv) respiratory difficulty with oxygen therapy, (v) lethargy and (vi) seizures within the first 72 hours of birth (9,24).

(b) Neonatal Jaundice:

It is one of the most common problems seen in term newborn children. Jaundice if presents within the first 24 hours immediately after birth is considered pathological. The aim should be to exclude any pathologic cause for jaundice and start phototherapy if the total serum bilirubin level rises above 15 mg per dL. If the treatment will be given at the appropriate time it will prevent the bilirubin neurotoxicity (25).

(c) Kernicterus:

It is the complex syndrome used to describe the neuropathology of brain injury follows bilirubin toxicity and its associated clinical findings. It cannot be defined only on the basis of total serum bilirubin (TSB) level. Kernicterus can be defined in term or near-term neonates with TSB $\geq$ 20 mg/dl, using abnormal muscle tone on examination, auditory testing diagnostic of auditory neuropathy or dys-synchrony and magnetic resonance imaging showing altered signal intensity of globus pallidus bilaterally with or without sub-thalamic nucleus involvement (26).

(d) Neonatal Seizures:

Neonatal seizures are epileptic fits occurring from birth to the end of the neonatal period in the absence of metabolic disorders such as hypoglycemia or hypocalcemia with no need for long-term treatment by any anti-epileptic medications. The early neonatal period, i.e. the first week of neonatal life, especially the first two days are the most vulnerable period when almost 80% of neonatal seizure occurs (24,27).

(e) Preterm:

The World Health Organization (WHO) has defined preterm as babies born alive before 37 weeks of gestation. There are sub-categories of preterm birth, based on gestational age: extremely preterm (<28 weeks) very preterm (28 to <32 weeks) and moderate to late preterm (32 to <37 weeks) (28,29).

(f) Hypoglycemia:

For newborn the blood glucose concentration should preferably be maintained at or above 47 mg /100 ml. Neonatal hypoglycemia is a feature of illness or of failure to adapt from the fetal state of continuous transplacental glucose consumption to the extra-uterine pattern of intermittent nutrient supply. It is more likely to occur in conditions where infants become cold or initiation of feeding is delayed or in cases of diabetic mothers (30).

(g) Neonatal sepsis

Neonatal sepsis has been defined variously as "the presence of pathogenic microorganism or their toxins in tissues or blood" as evidenced by positive blood culture during the 1st week of life with any organism known to cause neonatal sepsis or as "a harmful or damaging host systemic response to infection when the host response to infection becomes enhanced or deregulated." The International Sepsis Definition Conference (ISDC) in 2001 defined sepsis as "the clinical syndrome defined as the presence of both infection and systemic inflammatory response syndrome."(24,31)

CAUSATIVE FACTORS & THEIR PATHOPHYSIOLOGY IN CEREBRAL PALSY:

Complications during child birth, complications in the neonatal period and complications due to prematurity can lead to diffuse ischemic brain injury. This diffuse ischemic brain injury has been described by several terminology including perinatal asphyxia, hypoxic-ischemic encephalopathy and asphyxia neonatorum (32).

The damage occurred to the developing brain of may be prenatal, natal or postnatal. 75-80% of the injury is due to prenatal complications. Birth asphyxia or birth trauma leads to only 10% of case approximately. The risk of the brain injury and cerebral palsy is increasing with

decreasing gestational age and birth weight. A meta-analysis shows that 10-18% of babies born with a birth weight of 500-999 grams eventually suffer from hypoxia and ischemia related neurological abnormalities.

Indian studies have reported a few peculiar groups under etiology(i) prenatal maternal chorioamnionitis is an important risk factor accounting for as much as 12% of cerebral palsy in term infants and 28% in premature infants (ii) neonatal jaundice (iii) low birth weight (3).

Table 1: Etiological Risk Factors in Cerebral Palsy

No	Risk factor	Timing
1	Placental dysfunction or abnormalities	Antenatal risk factors
2	Major and minor birth defects	
3	Low birth weight	
4	Meconium aspiration	Intrapartum risk factors
5	Caesarean section	
6	Instrumental delivery	
7	Breech extraction	
8	Birth asphyxia	
9	Neonatal seizures	Neonatal Risk factors
10	Respiratory distress syndrome	
11	Hypoglycemia	
12	Infections including meningitis and sepsis	
13	Neonatal hyperbilirubinemia*	

* Neonatal jaundice is not considered as a potential risk factor in the medline search up to 31 July 2011 as per the Meta-Analysis of Observational Studies in Epidemiology guidelines (33).

Prenatal risk factors for CP are multiple pregnancies, placental complications, exposure to teratogenic agents; intrauterine infections and maternal conditions like seizures, mental retardation or hyperthyroidism. Perinatal risk factors include intracranial hemorrhages, ecclampsia, neonatal sepsis, hypoglycemia, prolonged hyperbilirubinemia, birth asphyxia and perinatal arterial ischemic stroke. Postnatal causes are trauma, infection like meningitis and encephalitis. The table 1 enumerates the etiological risk factors. (3, 34)

PATHOGENESIS OF CP:

The fetal brain undergoes complex organizational changes in-utero during development and the developmental process still continues ex-utero also. The pathogenic events which significantly affect the developing fetal brain can cause brain abnormalities or brain lesions. The pattern of the abnormality depends upon the exact stage of brain development during the time of insult to the fetal brain.

Cortical neurogenesis predominantly happens at the 1^{st} - 2^{nd} trimester of gestation. This cortical neurogenesis is predominantly characterized by proliferation, migration, and organization of neuronal precursor cells, then neuronal cells. Mal-developments caused by genetic or acquired impairments characterize the particular brain pathology (2).

The gross architecture of the brain is well established at the late 2^{nd} and early 3^{rd} trimester onwards. After the gross architecture of the brain is well established, growth and differentiation events predominate till birth and extend into the post natal life. The growth and differentiation events include axonal and dendrite growth, synapse formation, and myelination. Any insults of brain during this particular period of brain development will lead to lesions or defects. The causes of the insult are quite many and the important factors are inflammation with oxidative

stress, excessive cytokine production, triggering the excitotoxic cascade, excess release of glutamate, hypoxic-ischemic events and the consequences of infections (2).

Periventricular white matter is particularly damaged if the insult happens in the early third trimester or to the preterm born child. If the insult occurs at the end of third trimester of pregnancy or to a term born neonate gray matter is more vulnerable and predominantly shows the abnormal changes due to the damage happen. The gray matter includes the cortical gray matter and deep gray nuclei like basal ganglia and thalamus. Arterial territory infarcts particularly of MCA territory are seen mainly in term born cerebral palsy children although it may happen in very preterm (2).

Hypoxic ischemic brain injury and Cerebral Palsy:

Asphyxia, wherein there is impaired exchange of oxygen and carbon dioxide results in hypoxia, hypercarbia, acidosis and decreased systemic blood pressure. The hypoxia and hypercarbia causes loss of normal vascular auto regulation, resulting in pressure passive flow (34–36), and thus decreased perfusion of brain, which is seen as ischemic injury of term born infants and white matter injury or germinal matrix hemorrhage in preterm infants (38,39). Summarizing, birth asphyxia due to hypoxic-ischemic brain injury affects cardiac output, which in turn decreases brain perfusion causing global ischemia (38). The sites prone for hypoxic ischemic encephalopathy in term infants include cerebral cortex, peri-Rolandic cortex, paracentral lobule, hippocampus, visual cortex, thalamus, basal ganglia and brainstem (inferior colliculus and tegmental structures, including reticular formation and cranial nerve motor nuclei). Neuronal injury is often greatest in a laminar distribution in cortex, predominantly involving layers 3 and 5.

Varied degree & pattern of involvement is seen on neuroimaging and this correlates directly to the degree of asphyxia. In severe and total asphyxia, the pattern varies and is mainly confined to brain stem and deep gray nuclei. Ischemic insults predominate in the vascular end zones and border zones, thereby involving the neurons and premyelinating oligodendrocytes. Few examples of vulnerable vascular zones are as follows:

- Cerebral parasagittal cortex and white matter: End zone of ACA, MCA and PCA.
- Depths of cortical sulci: End zones of short penetrating vessels.
- Basal ganglia and thalamus, including posterior limb of the internal capsule: End zones of lenticulostriate, Heubner and posterior cerebral arteries.
- Brainstem: End and border zone in the vertebrobasilar system.

Affected cells show ischemic changes within the neurons after 24 to 36 hours, the important cytopathological features are marked eosinophilia of cytoplasm, condensation (pyknosis) or fragmentation (karyorrhexis) of the nucleus, loss of Nissl substance, breakdown of cytoplasmic and nuclear membranes often with apparent cell swelling. The affected neurons are shrunken and eosinophilic i.e. the classic red, dead neuron of ischemic injury.

The cerebral white matter damage may involve the sub-cortical and central regions as a component of parasagittal injury or it may involve the periventricular and central cerebral white matter, similar to periventricular leukomalacia seen in preterms. The main cellular target in periventricular leukomalacia is “premyelinating oligodendrocyte which most vulnerable to hypoxia-ischemia. Even though some degree of apoptosis can occur, majority of the cellular death in neonatal hypoxic ischemic encephalopathy is necrotic; following this event microglia is the prominent cell type, which is replaced by astrocytic response by 3 - 5 days. (41)

The important pathogenetic mechanisms are ischemia and inflammation for the

encephalopathy of prematurity, which is complex amalgam of primary destructive disease and secondary maturational and trophic disturbances. The preterm brain is intrinsically susceptible to excite-toxicity and free-radical accumulation which accentuate the vulnerability (39).

The flow chart (figure 1) briefly describes the cascade of important intracellular events with timeline and corresponding macroscopic effects and imaging appearances of the same. (40)

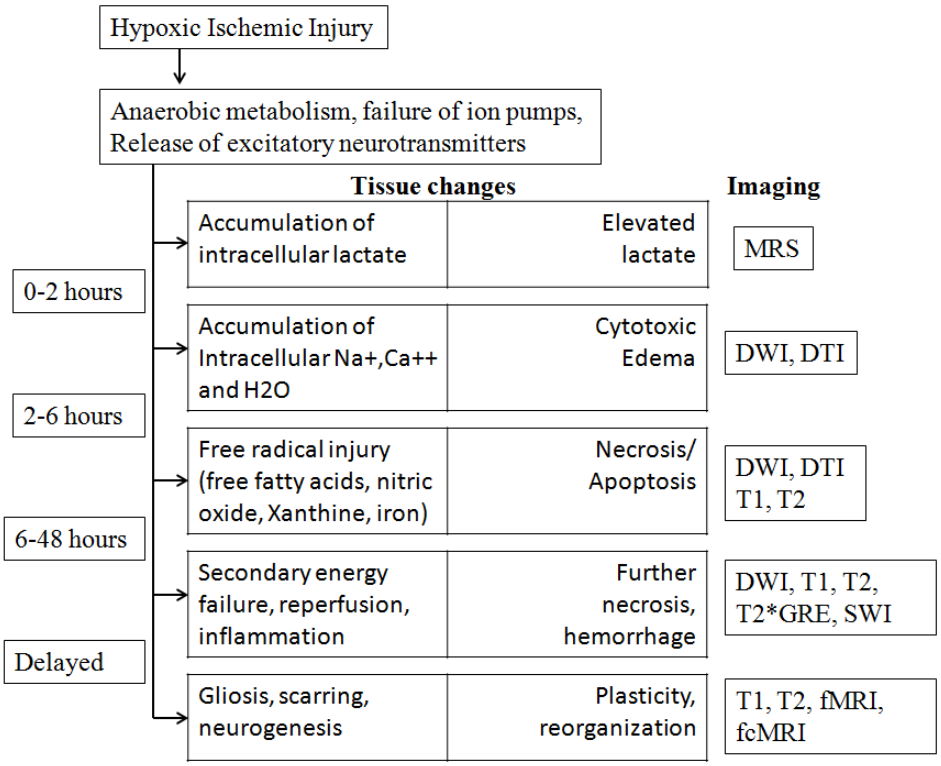


Figure 1: Hypoxic ischemic injury

MRS: Magnetic Resonance Spectroscopy DWI: Diffusion-weighted Imaging
DTI: Diffusion Tensor Imaging GRE: Gradient Echo sequence
fMRI: Functional MRI fcMRI: Functional Connectivity MRI
SWI: Susceptibility Weighted Imaging

Patterns of brain injuries in diffuse hypoxic ischemia:

Significant reduction in cerebral blood flow, oxygen, or glucose supply to the brain parenchyma result in hypoxic–ischemic encephalopathy (HIE). The reduction in blood flow is

global rather than focal in HIE. The duration of the insult and individual variables such as patient age and collateral circulation determine the pattern of brain tissue damage.

The consequences of hypoxic-ischemic episodes in the newborns and neonates can result in different patterns of brain injury. These different patterns can be best understood if interpreted as being the result of three primary factors: (i) maturity of brain at the time of injury; (ii) severity of hypotension; and (iii) duration of the event (34)

In preterm born neonates:

The neuropathology of encephalopathy of prematurity consists of periventricular leukomalacia and the associated neuronal and axonal disease. More advanced MRI techniques showed that cerebral white matter abnormality is accompanied by disturbances of gray matter structures. These abnormalities are located in the cerebrum, diencephalon, brain stem, and cerebellum. Only very recently it has become very apparent that these abnormalities of the neuronal-axonal unit are largely disturbances of development which would have been initiated by the initial injury. This constellation of white and gray matter abnormality is known as "encephalopathy of prematurity."(40)

In the developing fetus periventricular white matter is the vascular watershed zone and has a relatively high metabolic demand, rendering it susceptible to hypoxic-ischemia, especially in preterm children. Long-term sequel of periventricular white matter injury includes injury to corticospinal motor tracks and the geniculocalcarine tracts with involvement of the optic radiations leading to visual impairment, visual spatial perception and spastic diplegia (41,42).

Profound hypoxia in preterm born cerebral palsy children especially before 32 weeks of gestation shows damage to the thalami, basal ganglia and brain stem which can be detected by magnetic resonance imaging (43). So in profound ischemia the pattern of damage is similar to

the central pattern of injury as seen in term born children except by not involving a few peculiar sites like perirolandic cortex, superior cerebellar vermis and posterior limb of internal capsule. The reason why these three structure are not involved in preterm is they myelinate at term.

Mild to moderate asphyxia in preterm neonates leads to two common patterns

(a) periventricular leukomalacia (PVL)

(b) intracranial hemorrhage, including germinal matrix-intraventricular hemorrhage - GM-IVH (38).

In Term born neonates:

Two basic patterns of ischemic injury have been described in the term infant depending on the degree of asphyxia.

a) *Watershed infarct pattern of asphyxia*: Seen in infants with mild to moderate asphyxia, MRI shows cortical and sub cortical injury in the vascular watershed distribution with sparing of the deep gray nuclei and brainstem due to cerebral autoregulation (38).

b) *Central pattern of asphyxia*: Seen in infants with profound asphyxia, MRI shows involvement of the deep gray nuclei like basal ganglia, central myelinating structures such as hippocampi, ventrolateral thalami, putamen, dorsal brainstem, perirolandic cortex and superior cerebellar vermis with relative sparing of the cortex (44–47).

DIAGNOSIS:

Despite the large strides in the field of medicine over the years, particularly in terms of imaging and investigations, till date cerebral palsy remains a clinical diagnosis. The varied classification including the GMFCS system used in research is based on the clinical acumen,

needless to say the art of medicine still plays pivotal role in the diagnosis of cerebral palsy (14). Diagnosis till date is based by the developmental screening of all high risk babies, awareness of risk factors which increase the probability of CP occurrence and skilled neurological examinations. It is very important to examine the affected child in a systematic manner focusing on histories during obstetric and perinatal period, maternal history, review of developmental milestones and a complete careful neurological examination. Careful observation of the child in various positions such as supine, prone, sitting, standing, walking and running is necessary.

Early diagnosis of cerebral palsy poses diagnostic challenges before 6 month of age, however some cases of overt CP can be diagnosed much earlier than 6 months of age, and these infants have profound antenatal or perinatal insults with marked changes on MRI. Though clinical features are varied, some of the early manifestations are delay in the development mile stones and abnormal muscle tone. Perinatal and early neonatal history is crucial in such children as it enables differentiation from other illness which can be potentially treated such as slowly progressive white matter diseases as opposed to cerebral palsy which is "non-progressive in nature". Once acquired the mile stone will never show regression in children with cerebral palsy, however hypertonia eventually changes after 2-3 years into spasticity or dystonia.

Delay in the emergence of protective and postural reflexes, persistence of abnormal neonatal reflexes, spasticity or hypotonia of various distributions, asymmetrical movements like asymmetrical crawl, prominent fisting and hyper-reflexia are the described common early signs seen in the cerebral palsy child. Moro reflex, Asymmetric Tonic Neck Reflex (ATNR), Tonic and labyrinthine reflexes are the primitive reflexes, and presence of these are some of the most useful diagnostic tools at the time of clinical evaluation in diagnosis of Cerebral Palsy. In doubtful, equivocal or mild type cases careful observation over a period of time and repeated

thorough neurological examination will be required to get a confirmed diagnosis (3).

The important clinical findings to diagnose CP are:

- Delay in normal milestones
- Hyper-reflexia
- Muscle tone abnormality
- No regression of the clinical features
- No evidence of a more specific diagnosis.

In conclusion, when the aforementioned clinical features are found to be non-progressive, a diagnosis of Cerebral Palsy can be made with certainty. As the "non-progressive" component is deemed essential for the diagnosis of CP, judicious clinical judgment is imperative to determine how long to wait before labeling the child to have cerebral palsy (14).

The etiologic evaluation of cerebral palsy has several significant roles in the diagnostic evaluation including attempt to identify the probable cause of the child's disability and try to exclude the possible alternative diagnoses. For example to exclude dopa-responsive dystonia is very important because it responds very well to dopamine supplementation. Motor impairment and abnormal tone can be seen in inborn errors of metabolism where motor regression predominates, clinically motor regression can be seen as loss of skills. Unexplained hypoglycemia, recurrent emesis, or progressively worsening seizures are other important features of inborn errors of metabolism.

The clinician should be vigilant for the appearance of a late symptom that might suggest a more specific diagnosis especially in children with cerebral palsy ''of unknown etiology''. The table 2 enumerates the list of the main differentials in such clinical scenarios.

Table 2: Differential diagnosis for cerebral palsy

No	**Disorder**	**Important clinical feature**(14)
1	Familial spastic paraplegia	Typical family history
2	Transient toe walking	Deep tendon reflexes - present
3	Muscular dystrophy	Hypertrophy of calf muscles, positive Gower's sign
4	Metabolic disorders	Vomiting, neuro regression and lethargy
4a	Sjogren-Larrson	Ichthyosis
4b	Lesch-Nyhan	Severe self-mutilation
5	Mitochondrial disorders	Cardiomyopathy, unexplained hypoglycemia, multiple episodes of stroke
6	Genetic disorders	Multiple anomalies
6a	Miller-Dieker	Lissencephaly
6b	Rett Syndrome	Acquired microcephaly, hand wringing

IMAGING IN ISCHEMIC BRAIN INJURY:

Parents of children high-risk infants and children with motor delay or cerebral palsy seek information on cause, treatment, prognosis, and recurrence risk. Decades since the understanding of CP has moved on from the "typical" causative factors wherein perinatal events are accounted for, large strides made in the field of imaging technology, in particular MRI neuroimaging have revealed that in a significant number of cases the cerebral palsies have their origins much earlier on in pregnancy and indeed 9 to 17% are due to brain malformations, some of which are genetically determined (1–4). Neuroradiological evaluation of children with Cerebral Palsy with

MRI brain has not only attempted to provide a window to view the static lesion and but also has aided in gaining insight into the etio-pathogenesis of CP.

The American Academy of Neurology and the Child Neurology Society published a practice parameter in 2004 stating that all children with CP should have age-appropriate brain MRI. Krageloh-Mann et al reviewed studies done from 1990 to 2006, reporting that most almost 86% children with clinical CP had an abnormal MRI. In an Australian population-based study, 129 out of 154 (83.8%) of MRI studies were abnormal.(3) MRI brain is currently recommended to all Cerebral Palsy children.

However as enumerated above under the section of diagnosis in CP, there are variety of medical and congenital conditions including the dystonias and a range of neurometabolic disorders which may masquerade as CP, in such clinical scenarios, a normal MRI would be a definite indicator to consider other diagnostic possibilities, as these conditions have very different implications for individuals in terms of management and prognosis and for families in terms of risk of recurrence and heritability.

The main objectives of imaging in ischemic brain injury are:

(1) To confirm the presence of ischemia.

(2) Exclude other intracranial exigencies in the early neonatal period (USG plays vital role here).

(3) To determine the etiology and nature of the injury.

(4) To give treatment guidelines.

(5) To provide possible prognosis.

(6) To exclude congenital anomalies.

MAGNETIC RESONANCE IMAGING:

Last few decades have witnessed great number of advances in the field of neonatology, not only in terms of technological support, but also of advanced neonatal care, this in turn has resulted in efficient medical care of high risk newborn babies. However, on the contrary, this in no way has resulted in reduction of incidence of CP which has remained more or less the same over the last two decades.

However for the afflicted few incapacitated by the disease who were unable to live out their childhood, strides of advancement in the medical and rehabilitative interventions have made leeway to accommodate them within the ecosystem of our society. Limited understanding of the cause with recent research showing hypoxic insult to the developing brain may not be the only etiology, varied classifications which have evolved over the years, differences in the treatment plan and inconsistency in outcome have beset this clinical condition (48) **.**

With the advent of neuroimaging modalities particularly MRI with its ever evolving field of research strengthening the sequences and varied MRI functions such as spectroscopy, diffusion weighted imaging, fMRI and fibre-tracking, have begun to provide a foundation to address these problems, translating into real and anticipated benefits in care**.** Given the high yield from MRI of the brain in children with a clinical diagnosis of CP and the importance of new information for clinical management as well as sharing with families, there is today an international consensus statement on neuroimaging to be a part of the etiological work-up in those with clinical CP (49).

The increasing role of magnetic resonance imaging in the evaluation of cerebral palsy has been described extensively in literatures. The pathophysiological & morphological changes during brain development can be visualized in great clarity by magnetic resonance imaging.

Structural neuroimaging studies show that disorder specific findings in children with a wide range of developmental impairments prenatally and postnatally, functional modalities have been used to map regional cognitive processing and look for cortical plasticity. Though there is wide range of accepted medical and rehabilitative interventions for high-risk infants and children with cerebral palsy, there is often imprecise understanding of cause, variability in determination of treatment, and inconsistency in outcome. Over the period of the past decade, magnetic resonance imaging (MRI) and other neuroimaging modalities have begun to provide a foundation to address these problems, translating into real and anticipated benefits in care.

In seventy to ninety percent of children with cerebral palsy abnormalities have been found in brain MRI. When results are combined with history and neurological examination, imaging can give insights into etiology and pathogenesis, including patterns of selective vulnerability, thereby enhancing the treatment options, redefining prognosis and addressing issues of recurrence risks. In particular, this aids in diagnosing other diseases that masquerade as CP as imaging patterns of selective vulnerability specific to those particular acquired or genetic disorders can be seen, thus aid in improving the therapeutic options, improve prognosis and address issues related with recurrence risks (48).

T2W, T1W and fluid acquired inversion recovery (FLAIR) sequences evaluate the brain parenchyma and myelination status and they will guide to assess the brain maturity, volume loss, scarring, gliosis and abnormal T2 signal in the affected regions. When metabolic brain disorders are suspected MR spectroscopy can be a useful. Cerebral vasculature can be evaluated by MRA and MRV (MR angiography and MR venography) when perinatal stroke is suspected (38).

VARIED IMAGING MANIFESTATIONS OF CEREBRAL PALSY:

1. Periventricular leukomalacia (PVL):

The term periventricular leukomalacia was coined by Banker and Larroche in the year 1962, pathological studies have observed this finding of white matter damage following hypoxic-ischemic events in neonates as early as 1867. The term PVL has its origin from, leukos- white spots and malacia which means softening predominantly seen in the periventricular white matter. Histologically after initial insult, necrosis and cavitation develops which progresses to cysts. These cysts over time resulting in gliosis and reduction in the volume of periventricular white matter (32).

Antecedent to the present day advances in the field of neonatal neuroradiology, the bygone days were beset with elusive issues pertaining to the evaluation of preterm born neonate presenting with neurodevelopmental dysfunction. The present era of advanced neuroimaging has in fact unveiled the much debated issues pertaining to causative factors in the development of CP.

During the late 1970s, cranial ultrasound initially played a significant role. Subsequently, this modality was replaced by other imaging modalities such as computed tomography (CT) & MRI. The strength of CT is early diagnosis of bleed which led to emphasis on intraventricular bleed. This being a major source of disability in survivors of premature birth. CT is of limited utility in the imaging of PVL, MRI with its superior contrast resolution scores over CT in evaluation of PVL.

Neonatal cranial ultrasound, over the years has re-emerged with reinforced with better technology and is now being used not only in the detection of hemorrhage, PVL and other brain malformations, but also in terms of follow-up and prediction of probability of

neurodevelopmental dysfunction. Uniform consensus regarding the grading of PVL has not been reached. De Vries et al, proposed a classification in ’92, as enumerated below. This study also correlated the US findings with the MRI and found good correlation between the two modalities(50)

Grade I: areas of increased echogenicity, usually seen within 24h - 48h after an insult, that persists beyond day 7 but does not evolve into cysts.

Grade II: localized small cysts, predominantly in the fronto-parietal periventricular white matter.

Grade III: extensive cystic lesions, particularly in the parieto-occipital periventricular white matter. These cysts do not communicate with the lateral ventricles & resolve after several weeks. Follow-up cranial ultrasound in these children at 2-3 months of age do not reveal the presence of these cysts, however at this stage there is irregular ex-vacuo ventricular dilatation with wavy outline of the ventricles; secondary to atrophy of the periventricular white matter.

Grade IV: extensive cystic lesions extending into the deep (subcortical) white matter.

The preterm neonatal brain is most susceptible to the hypoxic-ischemic events and periventricular white damage in pre-term neonates is also known as “white matter injury of prematurity” (32), where the cerebral deep white matter injury was more severe than the superficial white matter injury. This pattern of white matter injury in the preterm neonates was established in the late 80’s and early 90s, with the advent of MRI (40). Preterm neonates are prone for hypoxic ischemic insults like perinatal asphyxia which leave the developing periventricular white matter (PVWM) of the preterm vulnerable to serious injuries; this in turn leads to a wide spectrum of motor and cognitive impairments in the surviving preterm infants.

Possible time of occurrence of this pattern of injury is around 23 to 32 weeks of gestation, insults to the brain during this period poses the greatest risk of periventricular white matter injury (7,8). In term infants this pattern of white matter injury is uncommon.

The predilection to particular regions of brain to hypoxic injury at different gestational ages is probably related to the differences in the maturity of cerebral vasculature and to the severity and duration of insult. However in recent times few studies have proposed a biochemical pathway to the mechanism of neonatal brain damage with involvement of factors such as tumour necrosis factor, role of free radicals and glutamate, transforming growth factor-β and the vulnerability of oligodendroblasts to these substances (51,52), thereby suggesting that the pattern of injury is could be related to the underlying pathological process rather than the gestational age per se (21). The prevalence of white matter injury of prematurity which was inversely proportional to the gestational age at which the child is born & the previous theory of ventriculofugal arterial territory injury is questionable now.

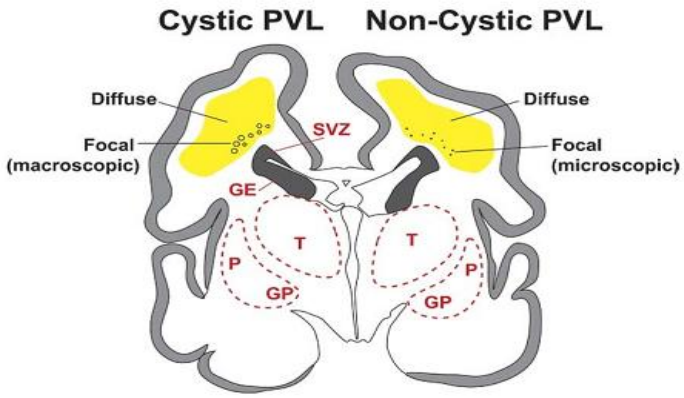
A recent study showed that cerebral white matter has low vascularity until after 32 weeks gestational age, suggesting that the relative hypovascularity of the periventricular white matter probably plays an important role in the development of PVL. This white matter injury is probably related to the vulnerability of oligodendrocyte to hypoxic injury. Because of the oligodendrocyte maturation after 32 weeks, it is observed that declining prevalence of PVL after 32 weeks of gestational age.

The periventricular leukomalacia consists of 2 major components. The first one is the focal necrosis deep in the white matter with loss of all cellular elements. And the second one is a more diffuse component affecting the central cerebral white matter.

The focal necrotic lesions usually tend to be relatively larger in size (more than few mm)

and form cysts of varying sizes finally. These cysts are imaged on neurosonogram or MRI brain. This type of white matter lesion occurs in only less than 5% of very low birth weight infants in modern neonatal intensive care units. The focal necrotic lesions generally evolve to small glial scars and are microscopic in size which is not easily seen on neuroimaging.

Injury to premyelinating oligodendrocytes occurs in diffuse type. It leads to marked astrocytosis and microgliosis (figure2). This consists either of cell death, loss of cell processes on viable cells or includes both. Hypomyelination with ventriculomegaly is the result of the above described types of injury. These two finding can be easily identified by neuroimaging. The failure of ensheathment of axons by premyelinating oligodendrocytes is an important cause of the hypomyelination (40).



- Cystic PVL (left): Focal necrotic macroscopic cystic lesions (circles)
- Non-cystic type: Focal necrotic microscopic lesions (dots) evolve to glial scars.
- Diffuse component (grey): Premyelinating oligodendrocytes injury, astrogliosis, and microgliosis.

GE: Ganglionic Eminence; GP: Globus Pallidus; P: Putamen; SVZ: Subventricular zone; T:Thalamus

Figure 2: Periventricular leukomalacia

Recent literatures have shown significant reduction in central white matter and subcortical neurons in infants with PVL resulting in volumetric decrease of the cerebral cortex

and thalamus, pathogenetic pathway for this is interlinked between hypoxia–ischemia and excitotoxicity pathway. The cerebral white matter axons like projection, commissural, and association fibers are in a phase of rapid growth at the peak period of vulnerability for periventricular white matter in the premature infant. Sub-plate neurons and late-migrating GABAergic neurons are the two principal neuronal types in the cerebral white matter during the premature period and these are critical for cerebral cortical and thalamic development, these are vulnerable to hypoxia–ischemia thereby causing volumetric deficits in the cerebral cortex and thalamus. Late-migrating neurons also may be intrinsically vulnerable (40).

The following flow charts describe the sequences of events in PVL (39,40).

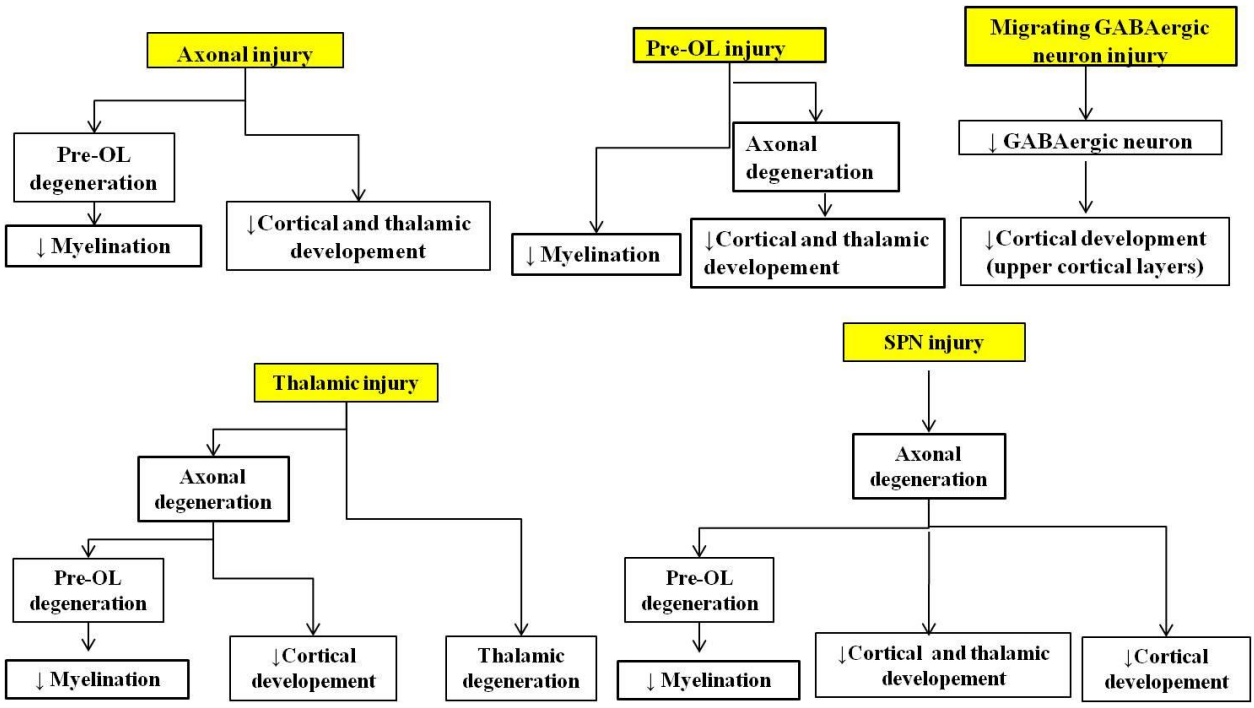


Figure 3: Important events leading to PVL injury

The causative factors of the above explained events could be the timing and nature of the insults, gestational age of the infant, associated critical factors such as exposure to

glucocorticoids or other drugs, disturbed nutritional state and many other unexplained factors (40).

The classic triad of PVL on MRI, visualized both on T1 and T2 weighted images, and was first described by Baker et al in 1988, consisting of

(i) ventriculomegaly with irregular outline of the body and trigone of the lateral ventricle;

(ii) reduced amount of white matter, especially at the level of the trigone, frequently also extending throughout the centrum semiovale and

(iii) deep prominent sulci, abutting the ventricle.

Summarizing, MRI findings of PVL include reduction in the periventricular white matter volume and volume of centrum semiovale, ventriculomegaly with ex-vacuo dilatation of the trigones, secondary to progressive necrosis of periventricular white matter, the ventricular outline appear irregular with an undulating wavy contour. These imaging findings appear early at trigone then extends to posterior periventricular white matter near occipital horns of lateral ventricles. In severe injury it extends anteriorly along the frontal horns and in profound injury there is significant white matter loss denoted by the gyri abutting the ventricular margins (38,53).

Cerebral palsy and PVL:

Percentage of periventricular white matter injury among the studied cerebral palsy cohorts described in literature is as follows:

(i) 31 % in the clinical and MRI correlates of CP in children who were born in Victoria, Australia by Robinson et al.

(ii) 47 % of the cases in the study done by Prasad et al. and

(iii) 42.5 % of the European Cerebral Palsy Study by Bax et al (6–8).

The table 3 summarizes the percentage of white matter injury and various clinical subtypes of cerebral palsy from the three important studies.

Table 3: Clinical subtypes of Cerebral Palsy and white matter injury

Study	Year	Diplegia	Hemiplegia	Quadriplegia
Bax et al.(6)	2006	71.3%	34.1%	35.1%
Prasad at al.(8)	2008	74.5%	11.1%	34.3 %
Robison et al.(7)	2009	47.9%	22.7% *	22.7%

* monoplegia also included

One recent study done by Serdaroglu G et al, correlated the severity of PVL on MR imaging and subsequent neurodevelopmental outcome in the children. Developmental tests were appropriate for age in 75% of patients with PVL I, but significantly delayed in all patients with PVL IV. Thinning of the corpus callosum and presence of cortical atrophy also correlated with neurological outcome (54).

2.Encephalomalacia:

The word encephalomalacia originates from the latin word "encephal" and "malacia" which means "softening of the brain". A diffuse insult to the brain in the late gestation, during child birth or in the early neonatal period results in multicystic encephalomalacia. The necrotic areas in the brain lead in the formation of multiple cystic cavities of varying sizes, separated by glial septations (55). Histopathologically, this condition is characterized by proliferation of astroglial cells, which lead to septations within the damaged brain.

Encephalomalacia is more common in term born children. The nature of the insult

determines the location of the lesions, thrombotic or embolic infarction leads to the distribution of the lesions in the territory of a major cerebral artery. On the other hand the hypoxic injuries resulting from mild to moderate hypotension will lead to the distribution of the lesions in the peripheral white matter and cortex in the watershed boundary zones. In cases of severe hypotension, only the immediate periventricular white matter may be spared. Deep gray nuclei injury is caused by profound hypotensive injury.

MR imaging features cannot characterize the cause of the injury. The reactive astrogliosis and tissue injury have areas of prolonged T1 and T2 relaxation & the loculations of fluid seen in cystic encephalomalacia on MRI appear as T1 hypointensity and T2W hyperintensity. The combination of variable sized glial septae and CSF within the lesion results in heterogeneity of the lesion on MRI brain. Fluid attenuated inversion recovery sequence (FLAIR) makes the heterogeneity of the lesion more obvious because it suppresses the CSF into dark signal and the glial strands appear hyperintense (55). Hence MRI is superior to CT in delineating the glial septae, enabling the same to be differentiated from other cystic lesions of the brain.

Cerebral palsy and encephalomalacia:

In a study done at the Royal Children's Hospital in Melbourne, Australia done by Robinson et al which studied a population based cohort of 154 cerebral palsy children, incidence of diffuse encephalomalacia seen in 14.3% (n-22). Out of the 22 children in this study 19 were term children and 13 of these children had spastic quadriplegia (7). In another study by Bax et al (the European Cerebral Palsy study) which evaluated 351 children, 33 (9.4%) had cortical and sub-cortical damage (this included cystic encephalomalacia with other cortical lesions). However this study did not throw any light regarding the increased incidence of encephalomalacia in term

vs. preterm group (6). The cerebral palsy study done by Prasad et al. reported a 29 % of encephalomalacia in a group of 102 children, this study added corroborative evidence to the RCH study at Melbourne, as there was a definite increase in prevalence of encephalomalacia in term born children vs. the preterm and these children has spastic quadriplegia(8).

3. Deep gray nuclei involvement:

Severe asphyxia results in a characteristic central pattern of injury in term neonates involving the deep gray nuclei, namely the putamina, ventrolateral thalami, hippocampi, dorsal brainstem, lateral geniculate nuclei and occasionally the perirolandic cortex (32). These are the actively myelinating areas in the brain of term neonates and thus have the maximum concentration of NMDA (N-methyl-d-aspartate) receptors (32) which are susceptible to hypoxia.

Few pathologic studies have demonstrated that the myelination of thalamus and globus pallidus occurs as early as 24-25 weeks of gestation age. However, the Caudate nuclei and putamen do not myelinate until 35-36 weeks gestation. The locations which show more advanced myelination are the parts of increased metabolic activity. These are the susceptible locations which tend to be damaged in the situation of oxygen deprivation. The relative sparing of perirolandic cortex in the preterm hypoxic child also has been explained by the above described hypothesis because the myelination of perirolandic cortex happens generally after 35-36 weeks (32).

Neonatal hyperbilirubinemia:

Neonatal indirect hyperbilirubinemia causes significant neurotoxicity, common etiologies being Rh and ABO incompatibility, G6PD deficiency and other unknown causes. The spectrum of neuropathological changes following the indirect neonatal hyperbilirubinemia is called as kernicterus. The clinical manifestations of Kernicterus are dystonia, choreo-athetoid movements, varying degree of hearing loss, restricted eye movements and developmental delay.

The typical pattern of neuropathological lesion in kernicterus symmetrically and selectively involves the basal ganglia. The most commonly affected areas by kernicterus are globus pallidus, subthalamic nucleus and hippocampus. The other rare areas affected by kernicterus are striatum, substantia nigra, thalamus, inferior olivary nuclei, cerebellar nuclei and various cranial nerve nuclei. Out of the cranial nerve nuclei the oculomotor, vestibular, cochlear and facial nerve nuclei can be particularly involved (56).

In MR imaging of child who had neonatal hyperbilirubinemia the salient and most commonly seen feature is bilateral symmetrical high signal intensity in the globus pallidus on T2-weighted images. Symmetrical signal intensity changes in the subthalamic nucleus on T2W images also have been reported in the cases of kernicterus (56). The other differentials of bilateral MR signal abnormalities of basal ganglia are hypoglycemia, inborn errors of metabolism, hemolytic uremic syndrome, osmotic myelinolysis, toxic exposures like cyanides and carbon monoxide poisoning and encephalitis (32).

Cerebral palsy and basal ganglia involvement:

Dystonic CP shows basal ganglia and thalamic damage which accounts for 75.6% (n=34) of the basal ganglia group in the European Cerebral Palsy Study. Spastic quadriplegic and diplegic children occasionally show this pattern of injury, however, none of the hemiplegic

children show this pattern of damage. Over all basal ganglia lesions include 12.8% of the total number of children evaluated in this study (6). A cerebral palsy study done in Melbourne, Australia shows nearly half of the cerebral palsy children have basal ganglia injury (7). Another study from Varanasi, India showed basal ganglia injury was seen in 13% of cerebral palsy children only of the study group of 102 children (8).

4. Corpus callosum:

Of the three interhemispheric commissures; the anterior commissure, the hippocampal commissure and the corpus callosum, the corpus callosum is the largest. Its development takes place in the 13^{th} week of gestation age. From this period of antenatal life the corpus callosum grows anteriorly and pushes the splenium posteriorly and the "c" shape happens about the 20^{th} week of gestational age. Further growth occurs by addition of fibers initially and myelination finally. The maximum size is attained at 6-9 years of age. It plays a vital role in interhemispheric connection and coordination and comprises about 19,00,00,000 axons approximately.

The corpus callosum has the following parts; rostrum, genu, body, isthmus, and splenium. These are the following connections of various parts of corpus callosum and different cortexes.

- Rostrum - fronto-basal cortex.
- Genu - prefrontal cortex and anterior cingulate area.
- Body - precentral (motor) cortex, insula, and cingulated gyri.
- Isthmus - primary auditory areas & precentral and postcentral gyri (motor, somatosensory)
- Splenium - medial temporal, posterior parietal and medial occipital cortices.

The corpus callosum is not myelinated at birth. By about 6 months of age after the myelination of cerebellum and genu of the internal capsule, the splenium of corpus callosum is myelinated; Genu is the last part of CC to be myelinated which happens at about the 8th month of infancy. After the 1st year of life the corpus callosum attains its complete signal characters; hyperintense on T1-weighted images and hypointense on T2-weighted images (57).

Corpus callosum has rich blood supply by both anterior and posterior circulations of circle of Willis. Anterior communicating artery (ACA) through the branches subcallosal and medial callosal arteries which deliver blood to the anterior part of the corpus callosum. Pericallosal artery supplies the body of corpus callosum. Posterior pericallosal artery, a branch of the posterior cerebral artery (PCA), supplies the splenium (57).

As described earlier, perinatal white matter injury especially in the preterm born neonates has been shown to have a broad spectrum of both radiological and clinical manifestations. These manifestations depend upon the gestational age of the neonate at which the insult occurred. Spastic diplegia is a common clinical manifestation of these pre-term children who suffered from perinatal insult. The corpus callosum is an important sensitive marker of destructive and dysgenetic processes in the central nervous system of children.

Ratios of CC in normal children were compared with the cohort of spastic CP children and statistically significant correlations have been made, the latter showed thinning of corpus callosum, this has been widely described in literature. The pathophysiology of callosal thinning seen in children with spastic diplegia is not clearly understood. Indirect axonal changes as a consequence of periventricular leukomalacia may be a reason for the callosal thinning in these suffered children. Diffuse loss of cerebral white matter, which is part of the diffuse component of

the neuropathological substrate of perinatal cerebral white matter disease, could be the probable cause of callosal thinning in this group of affected children with CP. Assessing cerebral white matter volume loss in the children with cerebral palsy and developmental delay has important prognostic implications. Many investigators have found that measuring the thickness of the various parts of corpus callosum on mid-sagittal T1 images is a rapid way to indirectly assess cerebral white matter volume (58).

Corpus callosum of neurologically normal children:

There is an exponential relationship with age of the thicknesses, length and overall area of the corpus callosum in the neurologically normal children. These parameters, thicknesses, length and overall area showed a steep increase in children up to 4 years of age. After which a constant and gradual increase was seen in children age group of 4-16 years.

However in a study done by Iai M et al, (10) ratios of the thickness of the mid body and of the splenium to the length were relatively constant in normal children of all ages. Therefore, these ratios obtained at the mid-body and splenium can be used as indices to assess the structure of the corpus callosum in children with the clinical diagnosis of cerebral palsy as opposed to the thicknesses wherein one has to match the values with normal of age. This study also proved that the length and area of the corpus callosum showed a linear relationship to age similar to that for thickness (10). The ratio of the thickness to the length of the corpus callosum in normal children group (n-69) as follows:

- Mid-body thickness/length 0.086 ± 0.014
- Splenium thickness/length 0.155 ± 0.018

Corpus callosal thickness and cerebral palsy:

Till date, various authors in the published literature have attributed the pathological mechanism of callosal atrophy noted in cerebral palsy, similar to the pathophysiology occurring in other white matter diseases like multiple sclerosis, trauma, infarction, and hydrocephalus, where there is direct damage to the axon or myelin, insufficiency in the micro circulation and wallerian degeneration.

But callosal thinning in cerebral palsy children is thought to be indirect axonal injury as a consequence of periventricular leukomalacia. The temporal and posterior superior frontal lobes (which are primary motor areas) probably supply the fibers composing the body of the corpus callosum. This mainly includes the white matter near the atrium of lateral ventricles which will be affected initially in the diffuse component of periventricular leukomalacia and maybe the cause why the body of the corpus callosum gets thinned out initially in the children with periventricular leukomalacia. In other words we can say that the thinning of corpus callosum would likely be secondary to the inability of these fibers to become properly myelinated because of damage to pre-oligodendrocytes.

The splenium of corpus callosum has fibers that come from the visual and visual-association areas of the cortex. These also can be affected by the focal component of periventricular leukomalacia. Fibers from the inferior frontal and anterior inferior parietal regions supplies the genu and these are the areas least affected by periventricular leukomalacia which explains the preservation of genu in many cases of severe periventricular leukomalacia, this has been described in cases where there is direct involvement of the corpus callosum as in cystic periventricular leukomalacia (58,10).

Panigrahy et al. shown that the positive correlation between the volume of the cerebral white matter and thickness of the mid-body of the corpus callosum in the children with cerebral palsy and developmental delay, regardless of their neuromotor or gestational age status (58). M Iui et al, reported that there is significant reduction in the thicknesses of the midbody and of the splenium of the corpus callosum in diplegic children as compared with the normal children. This study further stated that midbody and the splenium are the common sites of atrophy in the corpus callosum of diplegic CP, implying that in children with motor impairment there was a strong correlation with the degree of splenial atrophy. So in conclusion this study states that even though the level of impairment in corpus callosum is determined mainly by the severity of the motor pathway lesions, it can also be influenced by other brain functions, including visual cognition, which is related to the splenium of corpus callosum. The injury to the splenium and the visual-associated fibers near the peri-trigonal region may be the source of visual problems, such as strabismus, disturbed visual acuity and visual cognition dysfunction, that affect diplegic CP children (59,60).

5. Strokes and infarcts:

As opposed to the global ischemic injury seen in hypoxic ischemic encephalopathy, the ischemic injury commonly seen in patients with cerebral palsy is focal in nature and localized to a particular arterial or venous territory and manifests as perinatal stroke, these generally involve the term born infants. However, a few specific pattern of sinovenous thrombosis are also encountered often in preterm and near-term neonates.

Factors which can worsen the hypercoagulable state of the newborn like dehydration,

infection, instrumentation, hypoxia, birth trauma and infections of fetomaternal or placental origin, result in vascular thromboembolism. In these aforementioned clinical conditions, hypercoagulability of blood is due to immature coagulation cascade, this results in high blood viscosity leading to perinatal strokes. Arterial thromboembolism and perinatal arterial stroke are more commonly seen than perinatal sinovenous thrombosis (38).

Perinatal arterial stroke can develop as a thrombosis in the intra cranial artery or as an embolus from an extra cranial vessel, placenta or heart. The middle cerebral artery territory is the commonest site, and the left cerebral hemisphere is more commonly involved than the right side. Large solitary infarcts are commonly seen in the term infants who suffer from proximal MCA occlusion. In near term and pre-term born cerebral palsy child, distal MCA occlusion involving the cortical and lenticulostriate branches predominates & these infants particularly the preterm, multifocal infarct patterns are more common. Multifocal arterial ischemic injury also can be result of an embolic phenomenon.

Clinical presentation of perinatal arterial strokes either due to thrombosis of intracranial artery or embolus from extracranial sources is usually with neonatal seizures. On the other hand in cerebral venous thrombosis, the child is seriously ill and presents with encephalopathy and reduced level of consciousness. Many a time, this acute neonatal event is entirely missed, and it is only later in life when the child presents with significant motor deficits, developmental delay and seizures a preceding incident history maybe elicited.

Perinatal venous sinuses thrombosis often involves the superficial system rather than deep venous system, the reason being the superficial location of the dural venous sinuses which are highly prone for mechanical trauma during difficult child birth and any instrumental delivery. Intraventricular hemorrhage and thalamic infarcts are commonly seen in approximately 50 % of

affected children group with venous thrombosis. The other findings such as cranial fractures, subgaleal hematomas, and cranial suture diastases are the associated features especially in instrumental deliveries. In the children suffering from pre term or near term HIE, a large germinal matrix hemorrhage can compress the nearby medullary veins and cause thrombosis of them. This leads to venous infarct of the surrounding periventricular white matter.

MRI findings are increase signal intensity in T2W sequences, volume loss of affected arterial territory, wallerian degeneration and porencephalic cyst formation. Preliminary MRI images document an ischemic event, MR angiogram can help to find out the etiology of stroke. While most of the venous infarcts can be identified, the deep venous infarcts often present as signal intensity changes involving the basal ganglia and thalamic region, these are more difficult to diagnose. MR venogram is the investigation of choice of the neonate present with the acute signs of symptoms of venous sinus thrombosis. Follow-up MR venogram in many cases show complete absence of the main dural sinus with multiple collaterals.

Cerebral palsy and strokes:

One fourth of the children with hemiplegic CP in the European Cerebral Palsy Study showed a focal infarct which accounts for 27.5 % (n=25), however almost all children (n-25) with focal infarct had hemiplegia except one child which diagnosed to have quadriplegia (6). A population-based cohort of cerebral palsy children at the Royal Children's Hospital in Melbourne, Australia shows 25 children with a percentage of 16.2 had focal ischemia or hemorrhage. Out of these 25 children 16 were born term and 19 children had hemiplegic CP (7). Another study from Department of Pediatrics, Institute of Medical Sciences, Banaras Hindu University at Varanasi, India shows less common pattern of focal ischemic or hemorrhagic

pattern which included only 5.9% of the study group of 102 children. This study also revealed that focal ischemic or hemorrhagic lesion seen predominantly in term born children and hemiplegic CP children (6 out of 9) predominantly had this pattern of injury(8), further reiterating the increased prevalence of perinatal strokes in term infants.

6. Cerebellar involvement:

In association with periventricular leukomalacia especially in preterm born cerebral palsy children, cerebellar growth can be affected, as the cerebellum too is vulnerable to the effects of hypoxia-ischemia. Cerebellar insult secondary to hypoxic-ischemic events result in apoptosis. Literature draws a strong correlation of the cerebellar growth failure with supratentorial white matter lesions, especially in cases of periventricular leukomalacia. In premature infants with PVL, the pontine and inferior olivary nuclei which are the brainstem cerebellar relay nuclei show gliosis in 90–100%.

Interactions between the cerebellum and cerebrum probably occur through the cerebello–rubro–thalamo–cortical connecting fibers. Negative retrograde effects on cerebellar growth may occur due to significant thalamic disease of the premature CP children with PVL. Marked cerebellar growth failure in premature born cerebral palsy children has been almost completely confined to infants of less than 32 weeks gestation. Preterm cerebellar growth failure is most commonly seen in the premature children of 24–28 weeks gestational age. It has been documented that approximately three times increase in cerebellar volume happens during the 28 to 40 weeks' gestation (39).

7.Malformations and metabolic disorders:

Malformations:

Large strides made in the field of technology and imaging, in particular the field of MRI has increased awareness and it has now become apparent that a small group of cerebral palsy children after having undergone MRI have been found to have congenital brain malformations. Years ago, etiology of CP was attributed to only perinatal events, recent times, advances in neuroimaging have confirmed that a quite a significant number of cerebral palsy cases have their origin much earlier in the third trimester of pregnancy, about 9-17% of cases have congenital brain malformations, some of which are genetically determined (2, 58).

Malformation seen in the CP children described in literature includes lissencephaly, pachygyria, polymicrogyria, cortical dysplasia, heterotopias, cerebellar hypoplasia or dysgenesis, hydranencephaly, schizencephaly, holoprosencephaly, hydrocephalus, and corpus callosal agenesis (7). Malformation is more common in term infants (7,8). MRI feature suggestive of brain malformation in a cerebral palsy child warrants the consideration of an underlying genetic or metabolic etiology. As many of these malformations can be associated with specific genetic disorders for e.g lissencephaly with Miller-Dieker syndrome or chromosome 17p13.3, their diagnosis in the children who are affected indicates the further need of genetic counseling. Some metabolic disorders (e.g., peroxisomal disorders such as Zellweger syndrome) may have an association with cerebral malformations, and they can present within the first few years of life with a motor deficit that might appear to be non-progressive initially. However, till date, to our knowledge there are no studies which have evaluated children with CP with or without brain

malformations to find out the incidence of genetic or metabolic abnormalities in these subgroup (5).

Metabolic disorders:

Rarely metabolic disorders can masquerade clinically as CP. 30 children described from various small case series that ultimately developed clinical features of dyskinetic CP are due to glutaric aciduria (type 1). These particular type of disease affected children generally presented clinically by acute encephalopathy followed by dystonia, motor impairment and macrocephaly. More than half of the cases will have typical MRI features of frontal and temporal lobe atophy. As glutaric aciduria is treatable early diagnosis is important as significant motor and cognitive impairment can be prevented by early intervention and treatment. The other rare metabolic conditions include 3-methylglutaconic aciduria, Lesch-Nyhan syndrome, argininemia, pyruvate dehydrogenase deficiency, succinic semialdehyde dehydrogenase deficiency, cytochrome oxidase deficiency and female carriers of ornithine transcarbamylase deficiency can present with clinical findings suggestive of CP have been reported in small case series (5).

Cerebral palsy and malformations:

The three major cerebral palsy studies, Australian, European and Indian CP studies showed the percentage of cranial malformation as 12.3, 9.1 and 2.9 respectively (6–8).

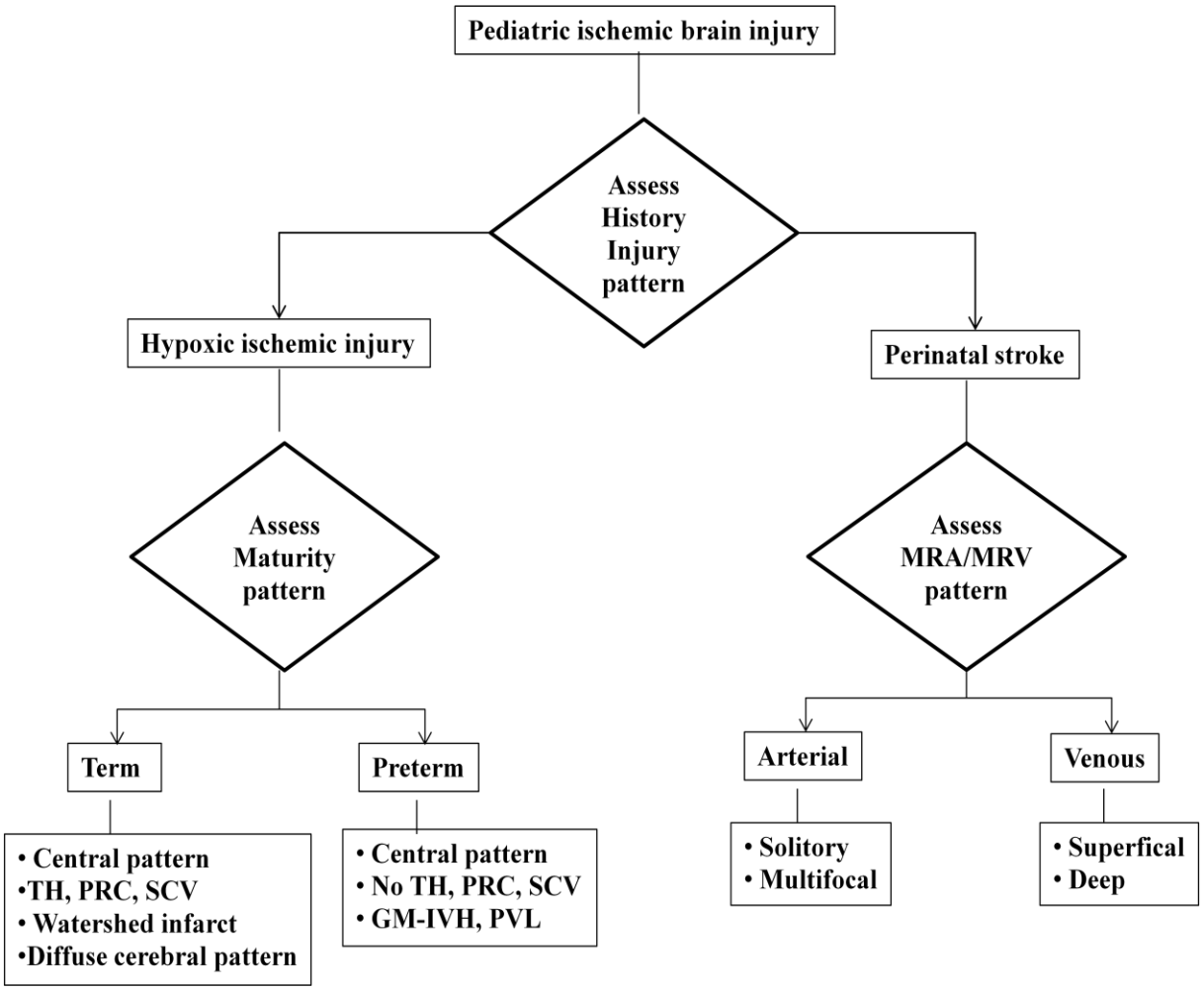


Figure 4: Radiological approach to ischemic brain injury (38)

TH -thalamus; PRC - perirolandic cortex; SCV - superior cerebellar vermis; GM-IVH germinal matrix intraventricular hemorrhage; MRA/MRV magnetic resonance angiography / venography

Management of cerebral palsy

In spite of recent advances in clinical medicine and research, the management approach to cerebral palsy has not seen significant change in the past few decades since promising neuro-restorative interventions such as stem-cell therapies are still in experimental stages. The importance and utility of specific strategies of intervention should therefore be clearly understood by the clinician so that pragmatic treatment goals can be discussed with the family.

Interdisciplinary or multidisciplinary rehabilitation team work is still the key factor in maximizing the functional abilities of the child. The team usually includes personnel from developmental pediatrics, pediatric neurology, rehabilitation medicine, pediatric neuroradiology, physical therapy, occupational therapy, speech therapy, childhood psychiatry, social work, nursing and special education. Goals of rehabilitation are usually directed at

- maximizing mobility functions as feasible- bipedal with or without use of orthoses/walking aids, or by use of wheelchairs
- maximizing independence in activities of daily living and self care needs
- ensuring appropriate education in regular or special schools as per cognitive status,
- remunerative employment when appropriate
- social reintegration in community/societal level participation (60)

Advances such as Botulinum toxin injection for management of spasticity, and advances in assistive technology have helped improve functional performance (61). Family centered care in individualizing the provision of management strategies by optimal use of resources is critical for all children with special needs.

MATERIALS AND METHODS

Study design: Elaborative study of the MRI findings in children with CP.

Study type: Observational study with retrospective collection of clinical data.

Setting:

Christian Medical College Hospital (CMCH) is a tertiary care centre located in Vellore, northern Tamil Nadu. The Department of Radiology acquired PACS (Picture Archival and Communication System) in the year 2000 and has currently 3 MRI scanners, including a 3T MRI. The Department of Developmental Pediatrics which was established in 1997 has an annual outpatient of 5500 where children with various neurological conditions are evaluated.

Inclusion criteria:

All children with clinical diagnosis of cerebral palsy referred by the departments of Developmental Pediatrics and Pediatric Neurology for MRI of the brain at CMC Hospital during the study period March 2012-October 2013 were included for the study.

Exclusion criteria:

The MRI studies which did not fulfill the given protocol (T2W axial, FLAIR, T2W coronal, T1W sagittal, DWI and SWI sequences) were excluded from this study.

METHODOLOGY:

Sampling:

Children with clinical features of cerebral palsy were subjected to detailed clinical evaluation, including history and examination at the Department of Developmental Pediatrics or Pediatric neurology as per the standard guidelines. They were classified clinically and then referred to the Department of Radiology for MRI brain. Following the MRI, each child was enrolled for the study; medical records were obtained for details regarding classification and perinatal history. The MRI brain was evaluated by the principal investigator and counter checked by senior consultant. Findings were duly recorded and tabulated for statistical analysis.

Magnetic Resonance Imaging:

(a) MRI scanner: MRI brain studies of the CP children in our institution were carried out in Philips ultra high field 3 Tesla MRI - Intera Achieva scanner.

(b) MRI coils: 3Tesla: SENSE-head 8 channel MRI coils were used

(c) MRI protocol: Table 4 below shows MR protocol – Sequences and technique

Sequences	Repetition Time TR	Echo Time TE	Flip angle	Slice Thickness	Slice Gap(mm)	Matrix	One Acq Scan time	Inversion Time TI
T2W axial	3000ms	80ms	90	4 mm	0.4 mm	436x265	0.06 min	
FLAIR axial	1100ms	125ms	120	4 mm	0.4 mm	288x160	3.18min	2800ms
T2W coronal	3000ms	80ms	90	4 mm	0.4 mm	436x265	0.06 min	
T1 Sag	8.4ms	3.9ms	8	4 mm	0.4 mm	272x143	3.07 min	
(DWI) axial	2419ms	68ms	90	4 mm	0	112x089	0.29 min	
(SWI) axial	15 ms	21ms	15	4 mm	0	200x160	1.12 min	

(d) Image Interpretation:

MRI images of children with Cerebral Palsy who were included in the study were evaluated and categorized based on severity of findings into grades using standard protocols. Each study was assessed and the principal investigator was blinded to the local report available on RIS (Radiology information system) as well as to the clinical diagnosis.

The various MRI features described in this study are periventricular leukomalacia, deep gray nuclei involvement which includes basal ganglia, thalamus and dentate nuclei, cystic encephalomalacia, perinatal stroke in the form of incomplete or complete arterial territory infarcts, corpus callosal thinning, ulegyria, perirolandic white matter involvement, cerebellar atrophy, malformation and miscellaneous findings.

1. Periventricular leukomalacia:

Grading used in this study is a modified version; evolved in line with the grading in infants by Sie et al (62) and by Iai et al (10).

Grade 0: No periventricular leukomalacia

Grade 1: Periventricular white matter hyperintensity confined to the peri-trigonal region.

Grade 2: Periventricular white matter hyperintensites that extend to involve the parieto-occipital region with focal white matter loss.

Grade 3: Periventricular white matter hyperintensities involving periventricular region, extending to both occipital and fronto-parietal region, mild ventriculomegaly with undulating ventricular margins and mild to moderate volume loss.

Grade 4: Extensive periventricular white matter hyperintensities with marked volume loss, marked ex-vacuo dilatation of the ventricles with prominent sulci that nearly abut the ventricles, little or no interposed white matter.

2. Cystic encephalomalacia:

Multiple cystic cavities of variable sizes separated by glial septations are formed in the necrotic area. The location of the lesion changes according to the nature of the insult.

Grade 0: No encephalomalacia.

Grade 1: Multicystic encephalomalacia

Grade 2: Severe macrocystic encephalomalacia; large cysts separated by glial septae, with minimal sparing of periventricular white matter.

3. Deep gray nuclei lesions:

Grade 0: No involvement of deep gray nuclei.

Grade 1: Altered signal intensity of the dorsolateral thalami, posterior putamina or posterior globus pallidus (mild)

Grade 2: Altered signal intensity involving any of these deep gray nuclei which extends anteriorly (profound insult)

4. Perinatal stroke:

Grade 0: No arterial or venous infarct.

Grade 1: Incomplete territorial infarct (distal branch involvement).

Grade 2: Complete involvement of the arterial territory (main artery involved).

5. Perirolandic white matter hyperintensity and volume loss.

6. Ulegyria.

7. Cerebral Malformations:

A small group of children present clinically as cerebral palsy may have MRI features of congenital malformations like polymicrogyria, cortical dysplasia, schizencephaly, corpus callosal agenesis / hypoplasia and lissencephaly.

8. Corpus callosal measurement:

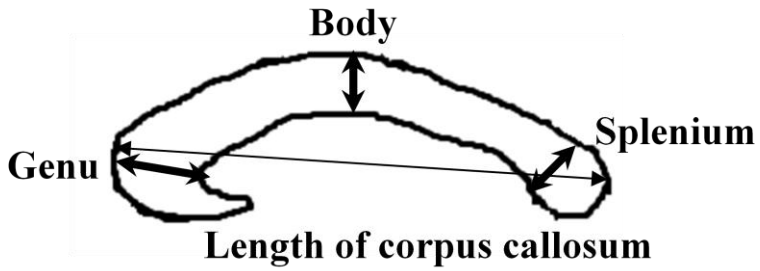


Figure 5: Schematic representation of corpus callosal measurements

The above diagram (figure 5) is a schematic representation depicting the part of wherein corpus callosal measurements have been obtained. Following the initial measurements; the ratio of the thickness of genu, midbody and splenium to the whole length of corpus callosum were calculated and values obtained were tabulated. These values were cross-referenced with the normal value range values described by Iai M et al (10). The corpus callosal thinning at the two major parts in mid-body and splenium were documented.

Institutional review board (IRB) approval:

Institutional review board (IRB) approval was obtained prior to the commencement of the study (IRB minutes number 8100 dated 05.12.2012 (Appendix 1).

Statistical analysis:

Data entered into epidata, version 3.1. Statistical analyses were performed using IBM SPSS Statistics software, a comprehensive tool for validated entry, documentation of data, calculation of frequencies and percentages, cross tabulation, Chi square test and analysis. (IBM Corporation, 1989, 2011), and $p < 0.05$ is considered significant.

Sample size:

The prevalence of abnormal MRI in CP has been described earlier in the introduction section (4–7). While studies show 70-100% of MRI's showing abnormalities, many studies show about 90% abnormal MRI and hence this number is used to calculate the sample size.

The sample size is calculated according to the following formula.

$n = Z\alpha^2 * p * q / d^2$

p – Proportion or prevalence

q – 100-p

d – Relative precision 5 %

Zα– Type 1 error of 5 % = α = 1.96 (95 % confidence interval)

Estimated minimum sample size needed in our study $= \frac{(1.96)^2 * 0.9 * 0.1}{(0.05)^2} = 138$

From the above sample size calculation a minimum of 138 patients were required. 210 children with a clinical diagnosis of cerebral palsy who were referred from the Developmental Pediatrics and Department of Pediatric Neurology for MRI brain were included in the study. (Two children who did not have the complete MRI protocol were excluded from the study.)

ANALYSIS AND RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL HISTORY:

i) Age and sex distribution: The mean age of the patient population was 4.31 years, the youngest in the study group was 6 months and the oldest was 15.5 years. 145 were male (69.05%) and 65 were female (30.05%). The following figures 6 depict the distribution of cases as per the age and sex groups.

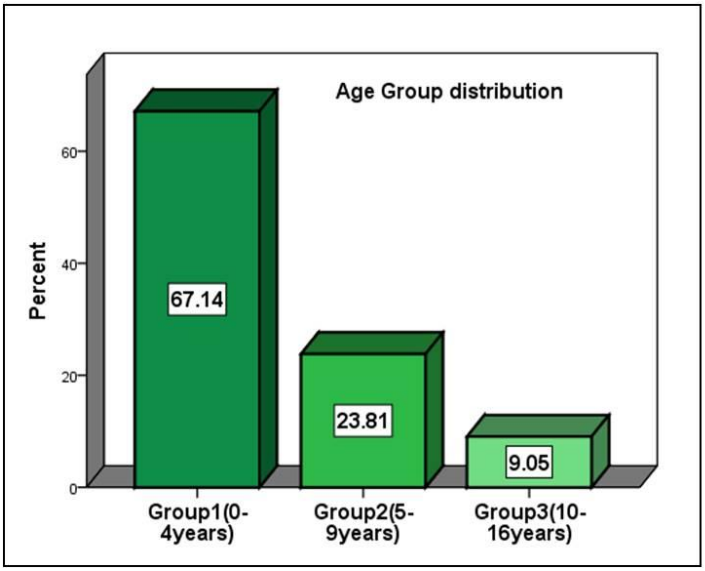


Figure 6a: Bar graph showing age groups

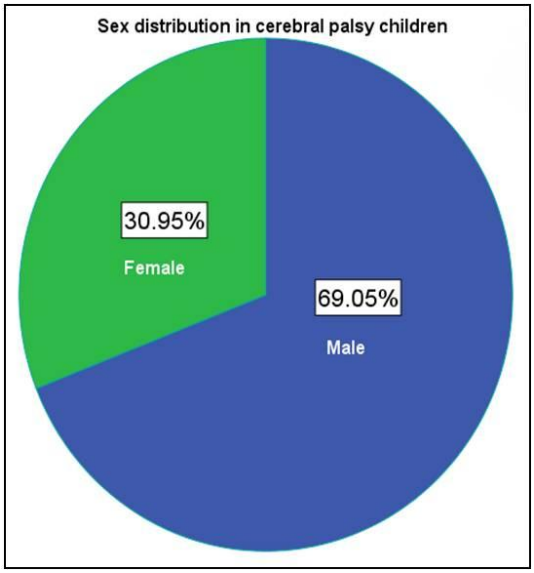


Figure 6b: Pie chart showing gender distribution

ii) Mode of delivery (birth history): 171 were hospital deliveries and 38 were home deliveries. Of the 171 hospital deliveries, 84 were normal vaginal deliveries, 77 cesarean sections (indication for LSCS – predominantly emergency for fetal distress, few for maternal causes and few were elective LSCS), 10 instrumental vaginal deliveries (vacuum and forceps). Perinatal details of 38 home deliveries were incomplete.

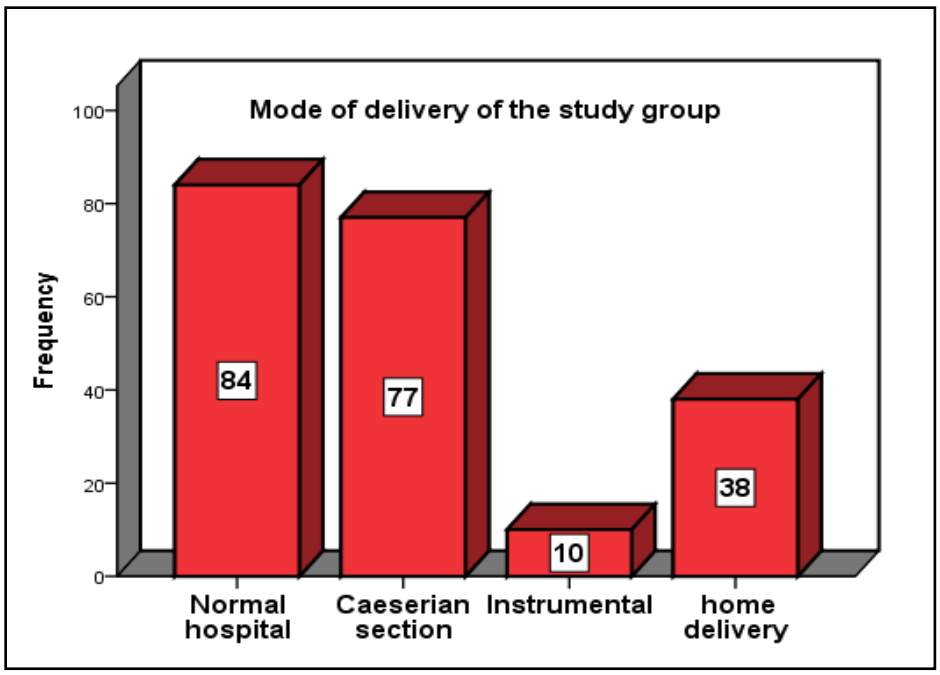


Figure-7: Bar graph showing mode of delivery

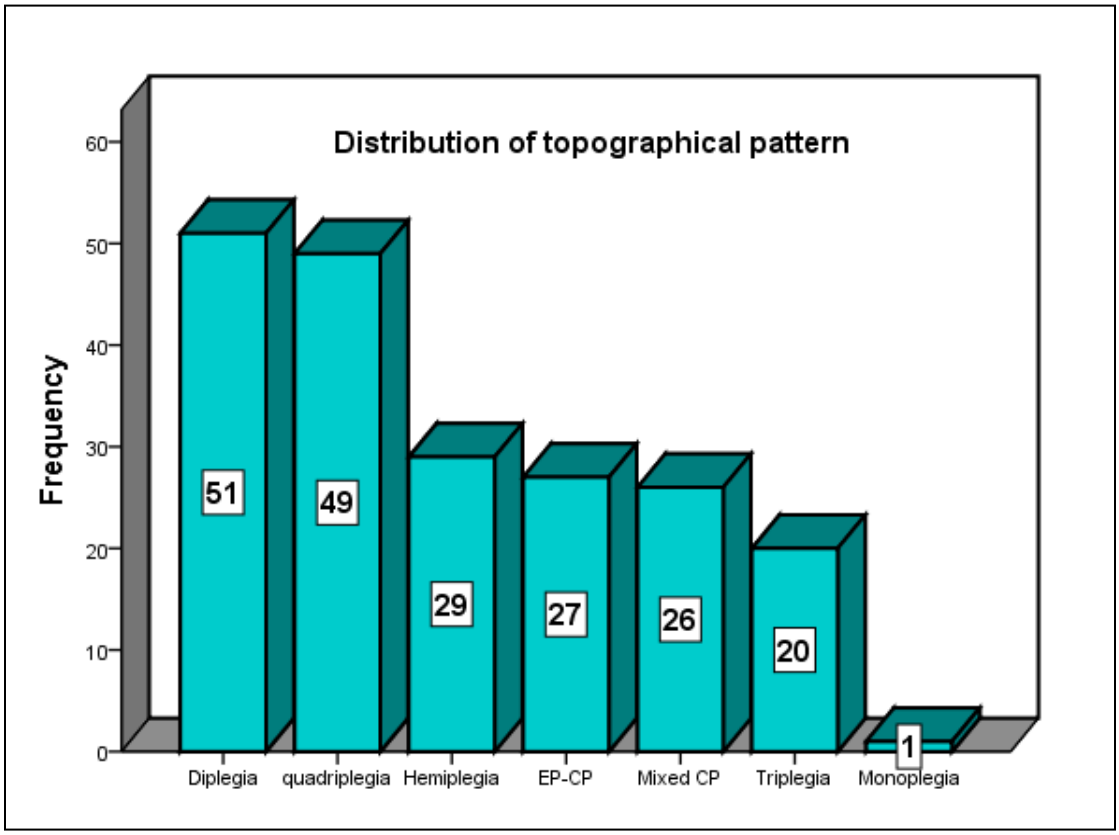


Figure 8: Bar graph showing distribution of topography of neurological deficit

iii) Gestational age: 139 (66.2%) CP children who were born after 37 weeks of gestation (term born) and 65 (31%) children were preterm born and 5 were post dated. One child was adopted; the birth history was not available.

iv) Perinatal history: 92 children had history of birth asphyxia, 75 had neonatal hyperbilirubinemia and 45 children had history of neonatal seizures.

Table -5: Showing summary of perinatal history

Perinatal History	**Hyperbilirubinemia**		**Seizure**		**Asphyxia**	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Absent	101	48.1	105	50.0	92	43.8
Present	**75**	35.7	**45**	21.4	**103**	49.0
Total	176	83.8	150	71.4	195	92.9
Data-N.A	34	16.2	60	28.6	15	7.1
Total	210	100.0	210	100.0	210	100.0

2. CLASSIFICATION BASED ON TOPOGRAPHY

a) **Clinical examination:** All the children were clinically evaluated at the Development Pediatrics unit and the Pediatric Neurology unit and were categorized based on topography (figure 8) and the neuromuscular deficits. Spastic were 148 (50 were diplegic, 49 were quadriplegic, 28 with hemiplegia, 20 with triplegia and 1 with monoplegia), extrapyramidal CP (EP-CP) was 27, Mixed (dystonic and spasticity) were 24, five were ataxic and 6 were categorized as hypotonic CP.

MRI PATTERN DISTRIBUTION:

In our study group of 210 children with CP 200 children had abnormal MRI brain (95.2%) and 10 children had a normal MRI brain (4.8%). Out of the 200 abnormal MRI 6 had only corpus callosal thinning, 7 had anomalies or malformations, 2 were post encephalitic sequel, 3 were metabolic disorders and 1 was a case of CMV infection.

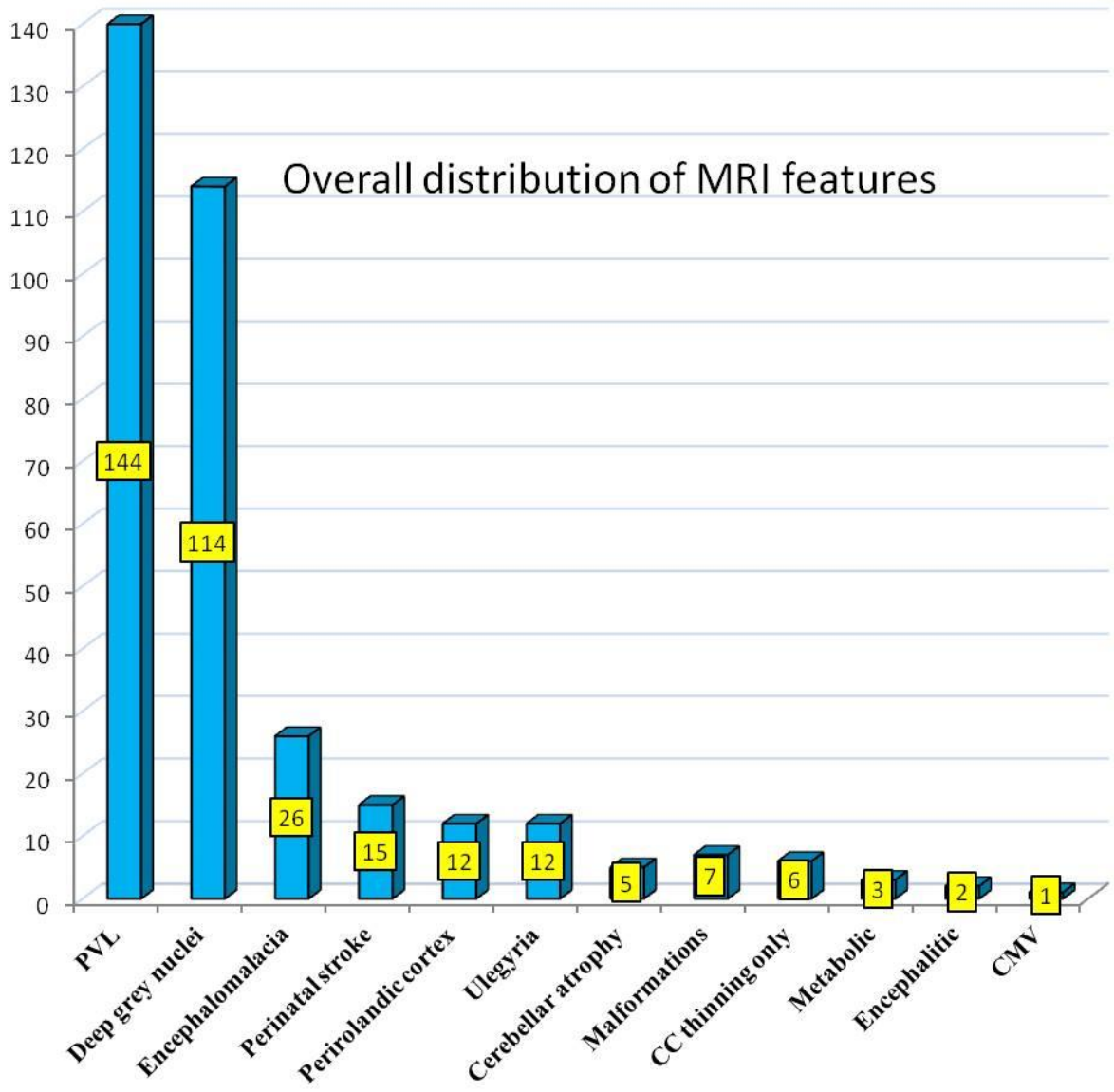


Figure -9: Bar graph showing distribution of various MRI abnormalities among the CP children

1) Periventricular leukomalacia:

(a) Frequency: This is the most common finding seen among 144 children (68.6%). Severity of PVL was graded from 1 to 4. Of the 144 children, grade 2 PVL was seen in 61, followed by grade 3 – 45, grade 4 in 21 and grade 1 in 17. 66 children had no PVL changes (Figure 10 and 11).

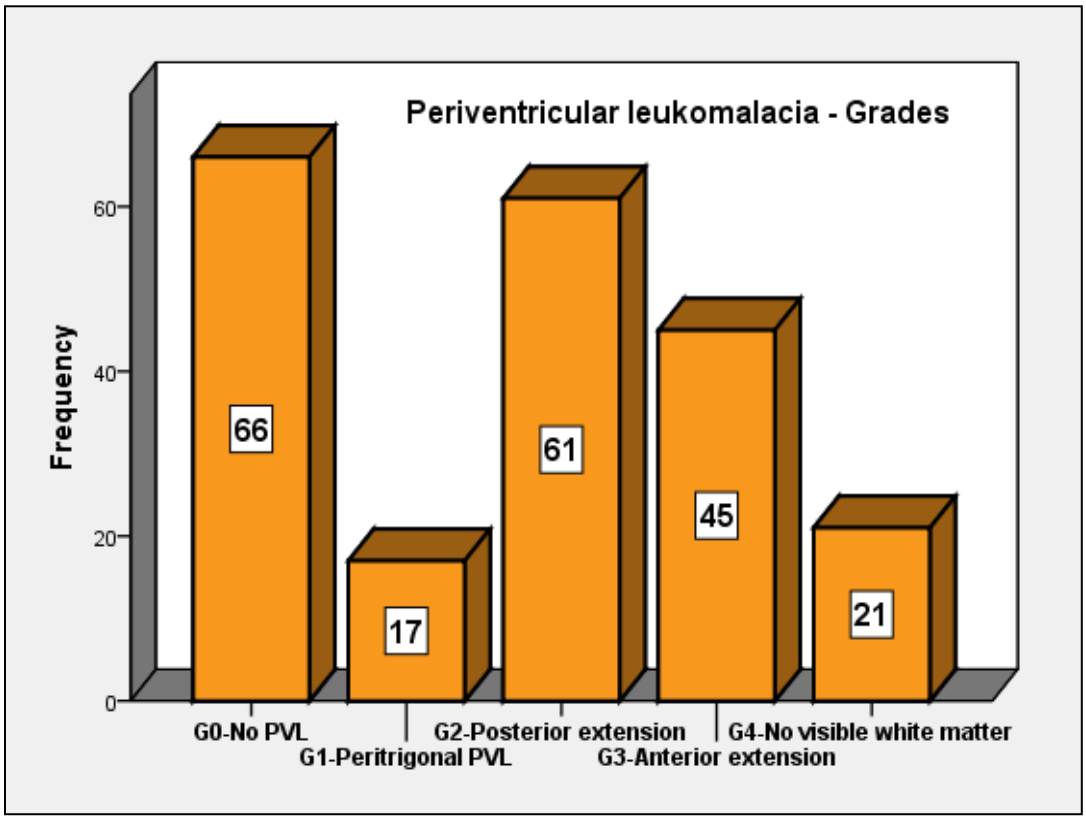


Figure – 10: Bar graph showing PVL grades

(b) PVL versus perinatal clinical history and examination:

[i] Gestational age & perinatal asphyxia: The frequency of PVL in preterm, term and post term children are depicted in figure 12. No statistical correlation between any groups of

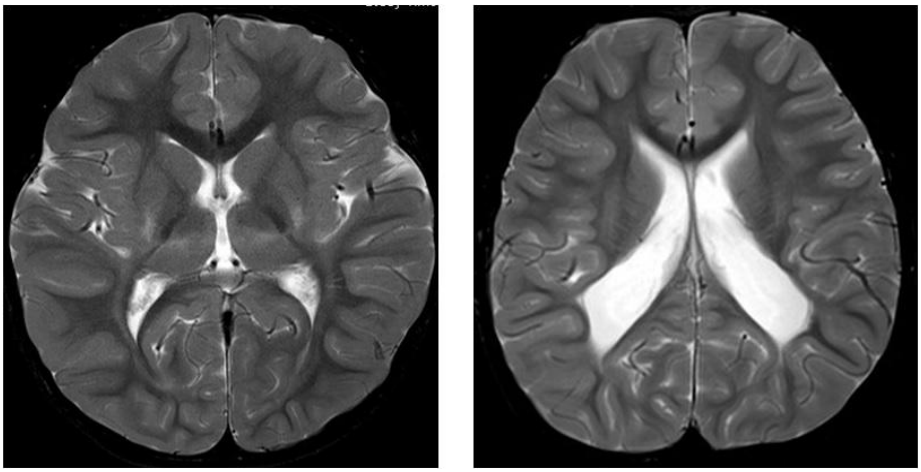


Figure – 11a: Grade 1 - Peritrigonal white matter injury; note the associated grade 1 deep gray nuclei injury where the posterior putamen and dorsolateral thalami shows T2W hyperintensity.

Figure – 11b: Grade 2 – Extension to the occipital periventricular white matter as evidenced by white matter volume loss and dilated lateral ventricles, particularly the occipital horns

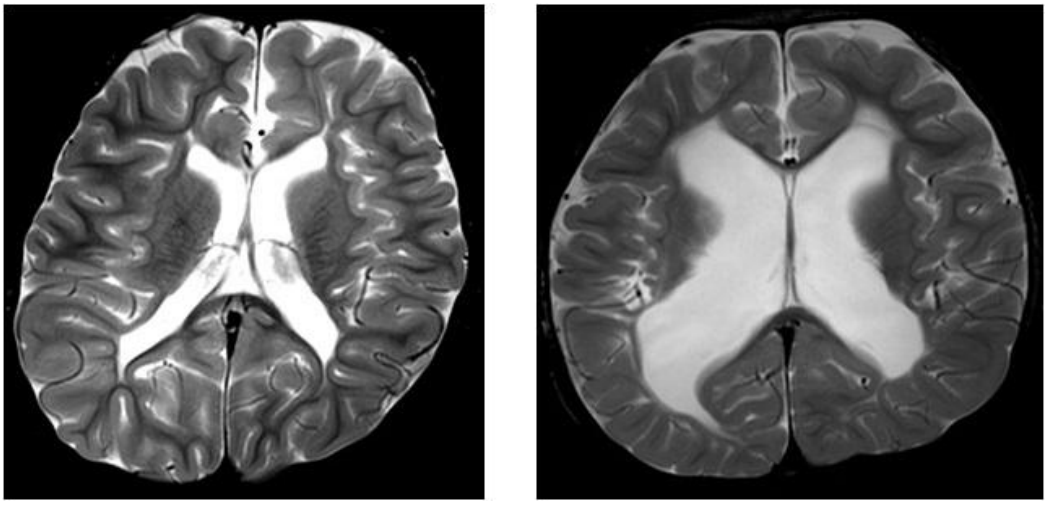


Figure – 11c: Grade 3 PVL - Involvement extends to frontal region.

Figure – 11d: Grade 4 PVL - Profound white matter loss - The gyri abutting the ventricles

gestational age with PVL (p=0.83). Asphyxia and PVL also do not have any statistical correlation between (p=0.11).

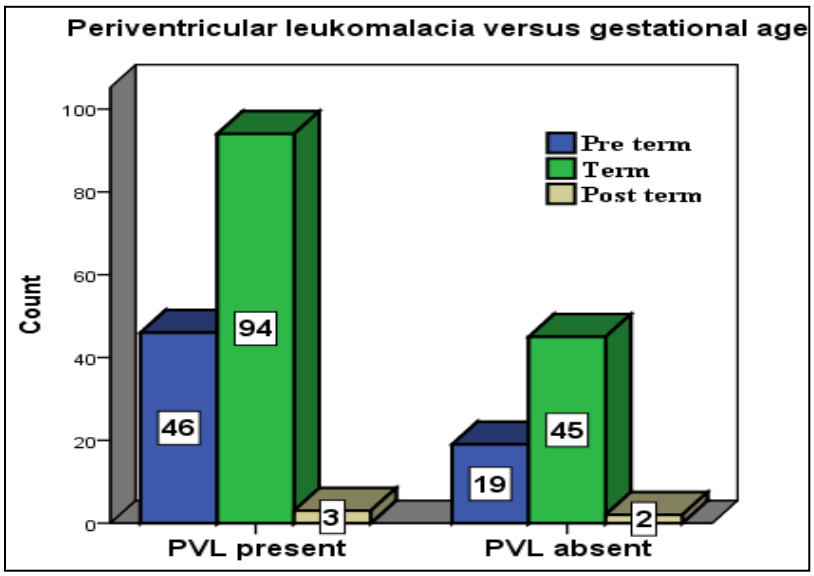


Figure – 12: PVL Versus gestational age

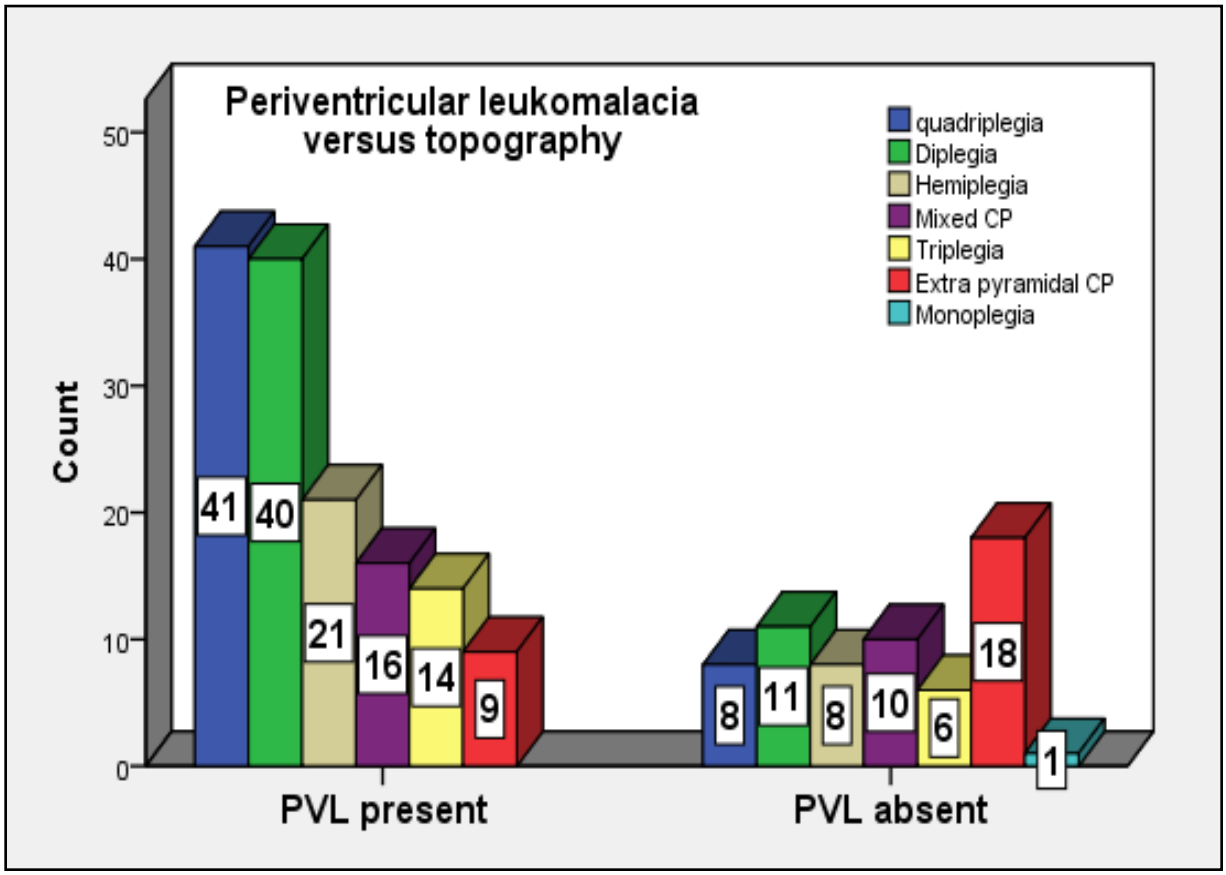


Figure 13: Bar graph showing distribution of PVL in various topographical patterns

[ii] Topographical patterns and distribution of PVL (figure 13): Among the 44 quadriplegic CP children 41 (93.2%) had PVL. 40(80%) out of 51 diplegic CP children, 21(72.4%) out of 29 hemiplegic CP children, 14(70%) out of 20 triplegic CP children, 16(61.5%) out of 26 mixed CP children and 9(33.3%) out of 27 extrapyramidal CP children had evidence of periventricular leukomalacia in the MRI.

Statistically there is equal distribution of PVL grades noted among the major four topographical patterns, diplegia, quadriplegia, hemiplegia and Triplegia ($p<0.0001$). Table 6 gives the frequencies of every grades of PVL in all 7 topographical patterns.

Table no – 6: Periventricular leukomalacia grades – Topography; Cross tabulation

PVL Grades	Topography							Total
	Diplegia	Quadriplegia	Triplegia	Hemiplegia	Monoplegia	EPCP	Mixed	
No PVL	10	3	6	8	1	18	10	56
G- 1	2	4	2	3	0	2	3	16
G- 2	18	11	6	11	0	7	7	60
G-3	16	10	5	7	0	0	6	44
G-4	4	16	1	0	0	0	0	21
Total	50#	44‡	20	29	1	27	26	197*

- One CP child who had congenital anomaly was excluded

‡ - 5 children who had congenital anomaly were excluded

* - The 7 congenital anomalies, 4 ataxic CP and 2 hypotonic CP children were excluded in the table

2) Deep gray nuclei involvement:

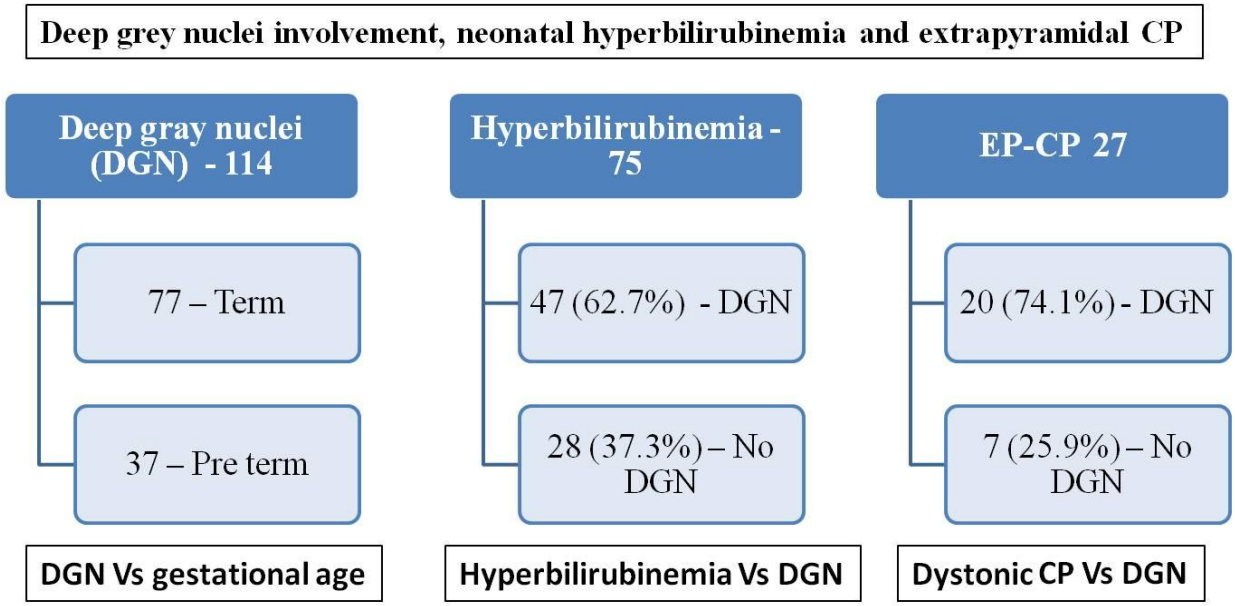


Figure 14: Different correlations in deep gray nuclei involvement, neonatal hyperbilirubinemia and extrapyramidal CP

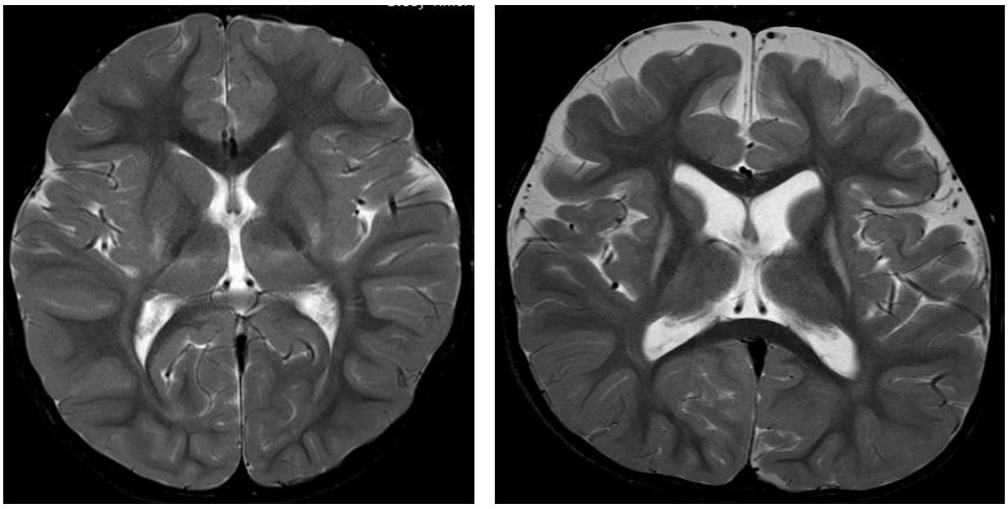


Figure –15a: Grade 1 deep gray nuclei involvement as evidenced by T2W hyperintensity of posterior putamen and dorsolateral thalami. **Figure –15b:** Complete T2W hyperintensity of putamen with atrophy - Grade 2 Deep gray nuclei involvement

Deep gray nuclei involvement versus perinatal clinical history and examination:

This is the second most common finding on MRI seen in a subset of 114 (54.29%). Of these 114 children, 77 (53.1%) were term CP and 37(57.8%) children were preterm CP. Of the 75 children with history of hyperbilirubinemia 47 (62.67%) of them had involvement of the deep gray nuclei. Of the 27 children who had extrapyramidal cerebral palsy, 20 (74.07%) children had deep gray nuclei involvement. (Figure 14)

3) Cystic encephalomalacia:

Cystic encephalomalacia (figure 16) was seen among 26 children (12.4%). Of these 26 cases, 19 (73.1%) were term born and 7 were preterm. Findings of cystic encephalomalacia predominated in the topographically classified quadriplegic and hemiplegic CP children, 9 and 7 respectively. However, none of the extrapyramidal cerebral palsy children had MR features of cystic encephalomalacia.

4) Perinatal strokes:

Perinatal stroke in the form of incomplete or complete arterial territory infarct was seen more common among the hemiparetic topographical group (figure 17). This pattern of involvement was noted in 15 (7.1%) children. Of these 15 children with features of arterial territory infarct 11(73.3%) had hemiparetic CP.

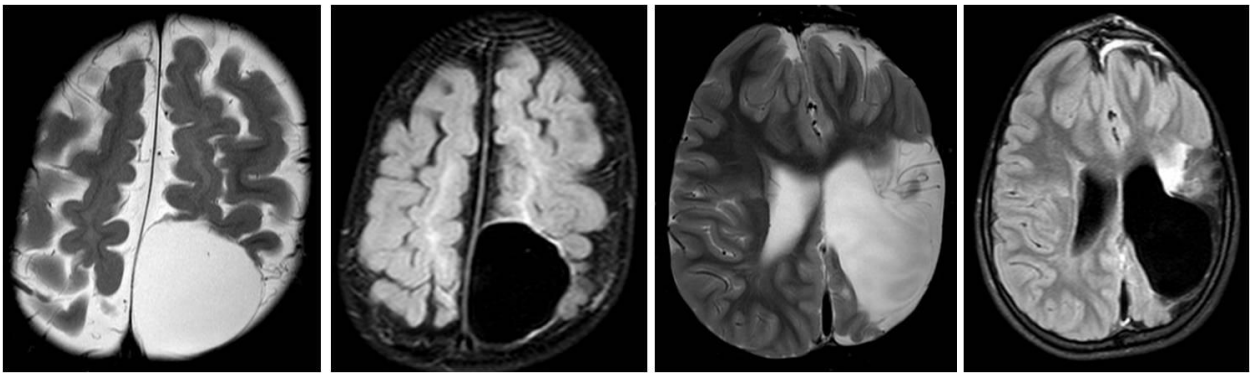


Figure –16a-d: T2W axial and FLAIR images of two children with cystic encephalomalacia

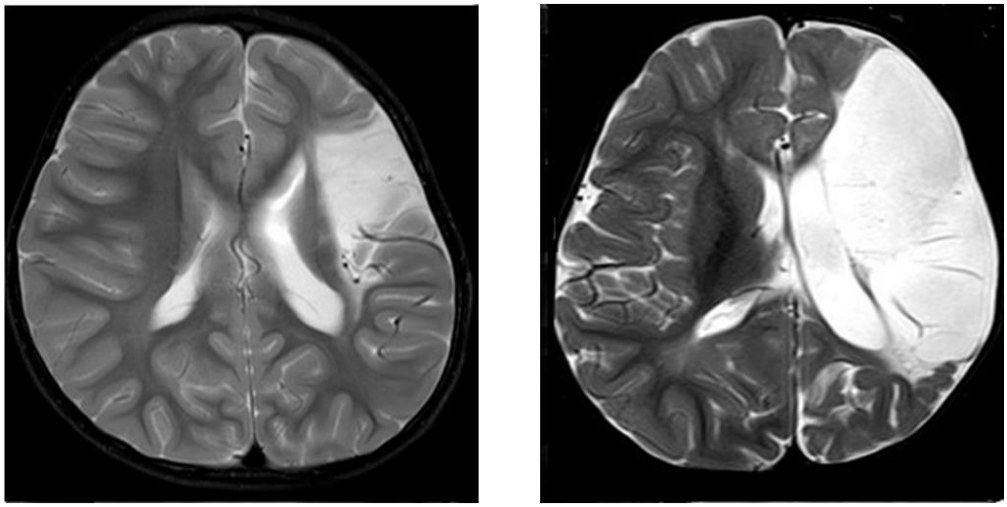


Figure –17a and b: Two different cases of left MCA territory infarcts

5) Perirolandic cortex involvement:

Of the 210 children with cerebral palsy, only 11 children showed evidence of perirolandic cortical involvement, 9 of who were term born children and 2 were preterm (Figure 24). This is a very small group for statistical analysis. Still term born children are more prone for perirolandic cortical involvement which is a well known entity.

6) Malformations:

Of the 210 cases evaluated, only 7 children (4.8%) had MRI features suggestive of malformation. The salient features are tabulated as below. Five of them had spastic quadriplegic CP. Vermian hypoplasia had presented as ataxic CP and the case of callosal dysgenesis had associated CVJ anomaly and presented as spastic diplegic CP.

Table -7: Locations of malformations (Refer to figure 18)

S. No	**Cerebral cortex**	**Ventricles**	**Corpus callosum**	**Posterior fossa**
1	polymicrogyria	Ventriculomegaly		
2		Enlarged ventricles Inter hemispheric cyst		
3	Schizencephaly Pachygyria		Agenesis	
4				Vermian hypoplasia Cerebellar atrophy
5			Dysgenesis	
6	Polymicrogyria Pachygyria lissencephaly			
7			Hypoplasia	

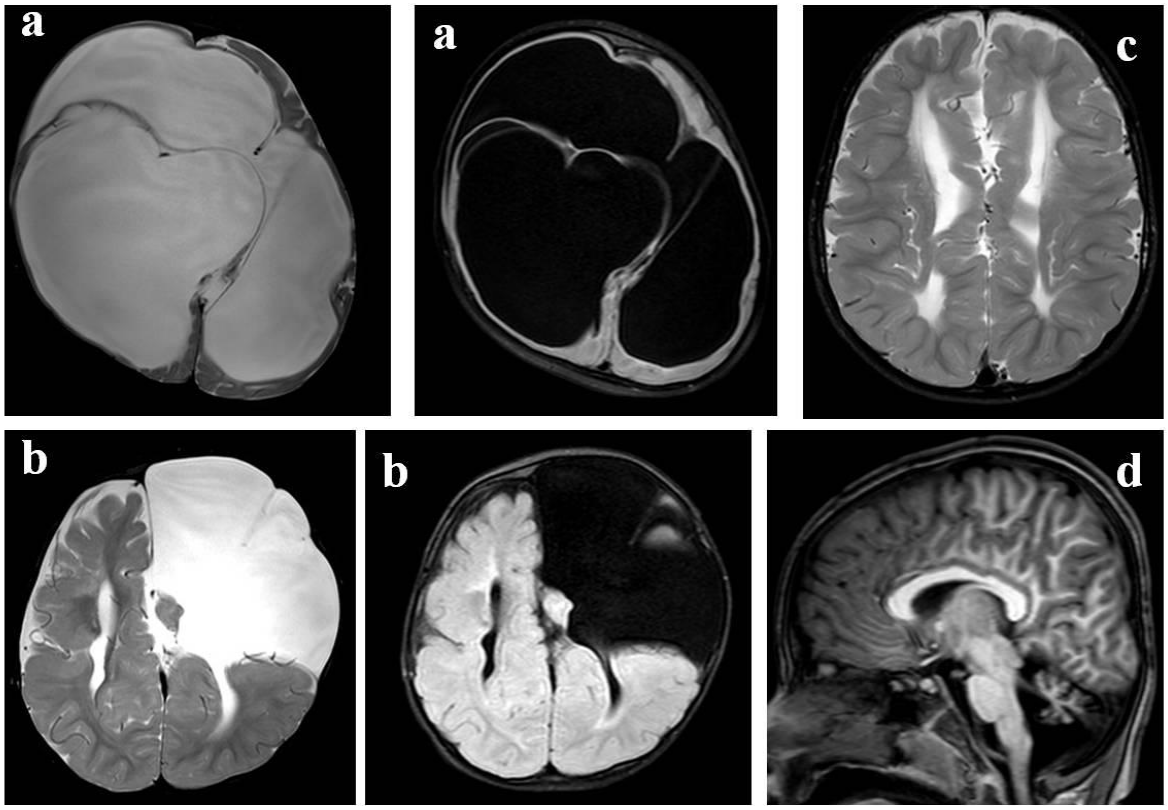


Figure – 18a-d: Few congenital anomalies presented as spastic quadriparesis. a –Interhemi-sphereic cyst with trapped lateral ventricles; b- open and closed lip schizencephaly; c- Corpus callosal agenesis; d-Vermian hypoplasia with cerebellar atrophy (This child had ataxic CP)

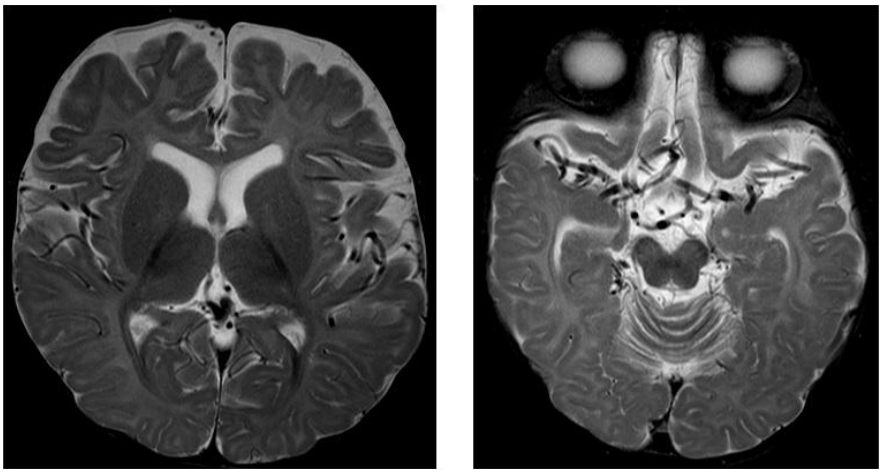
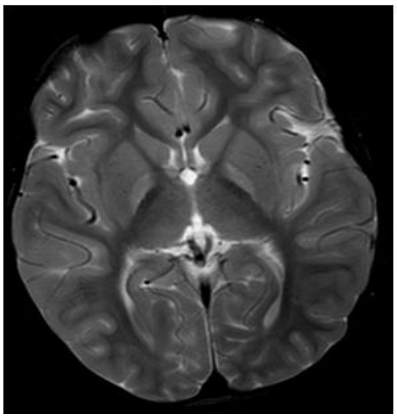


Figure – 19a, b: Tortuosity of the cerebral vessels**,** delayed myelination and globus pallidus hyperintensity- Menkes Kinky hair syndrome

7) Metabolic disorders:

Three cases of metabolic disorders presented as cerebral palsy initially. The figure 19 shows a case of Menkes Kinky hair disease; imaging showed tortuosity of the cerebral vessels**,** delayed myelination and globus pallidus hyperintensity. The figure 20 shows a case of G6PD deficiency clinically had kernicterus, on MRI showed grade 2 deep gray nuclei involvement as evidenced by complete T2W hyperintensity of globus pallidus. Figure 21 shows a case of Leigh's disease presented as quadriplegic CP who had complete T2W hyperintensity of putamen.



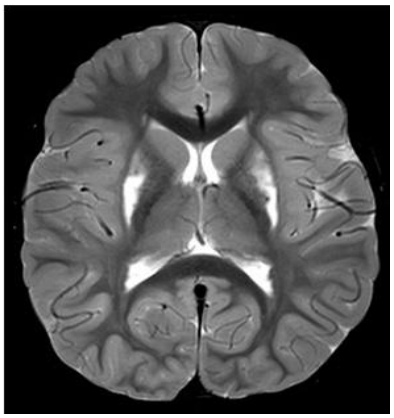


Figure – 20:
G6PD deficiency

Figure – 21:
Leigh's disease

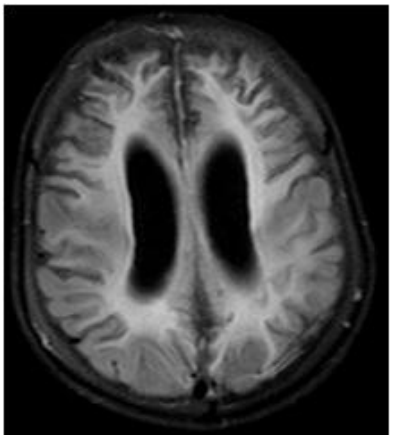


Figure – 22:
Post encephalitic sequel having diffuse abnormal signal and gyral thinning

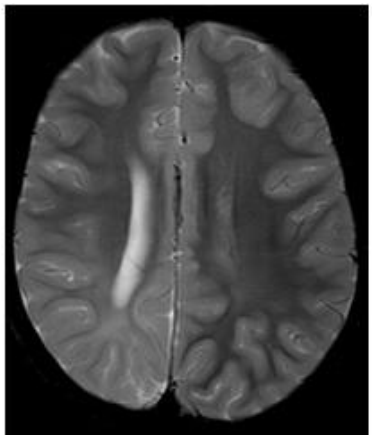


Figure –23:
Mild right hemiatrophy with right parietooccipital hyperintensity – a case of Rassmussens' encephalitis

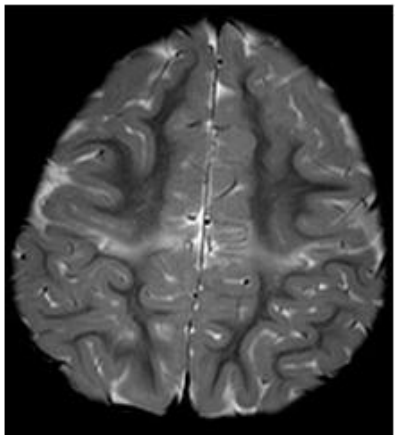


Figure –24:
Perirolandic cortical gliosis in a term born CP

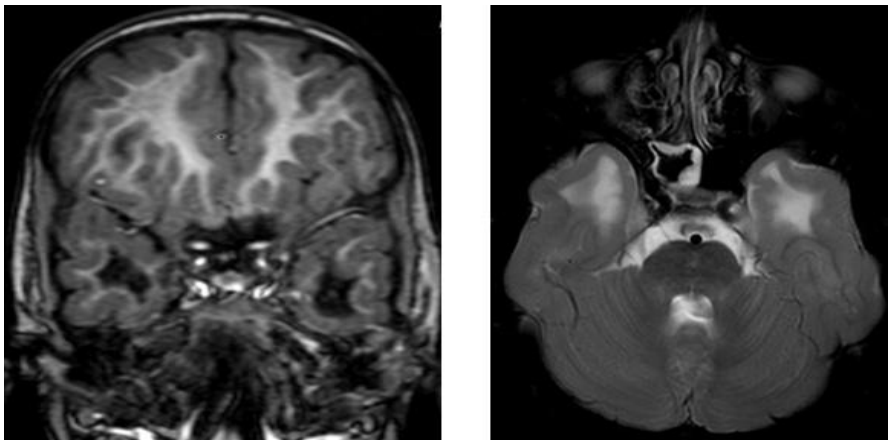


Figure – 25 Rash, Coarctation and Salt-pepper retinopathy; MRI shows Temporal lobe vacuolation cyst. CT (not shown here) shows basal ganglia and left parito-fronto-occipital calcifications – CMV infection

8) Miscellaneous findings:

- Cerebellar atrophy was seen only in 5 cases, of which 4 were term born.
- Among the 12 children who had Ulegyria 9 (75%) were term born.
- Five children had periventricular and parenchymal calcifications as additional finding, one of these was found to have cytomegalovirus (CMV) infection (Figure 25).
- Other MRI features like hemiatrophy of cerebral hemisphere and Rasmussens' encephalitis was also noted, these features are suggestive of post infective or encephalitic sequel (Figure 22, 23).

CORPUS CALLOSAL MEASUREMENTS:

The ratio of the thickness of midbody and splenium with respect to the length of corpus callosum were obtained for 204 children; three children had marked callosal atrophy rendering the caliper placement technically difficult. Six children with brain malformations either involve the corpus callosum or made the measurement not possible were excluded. (That makes the number of cases measured was 204)

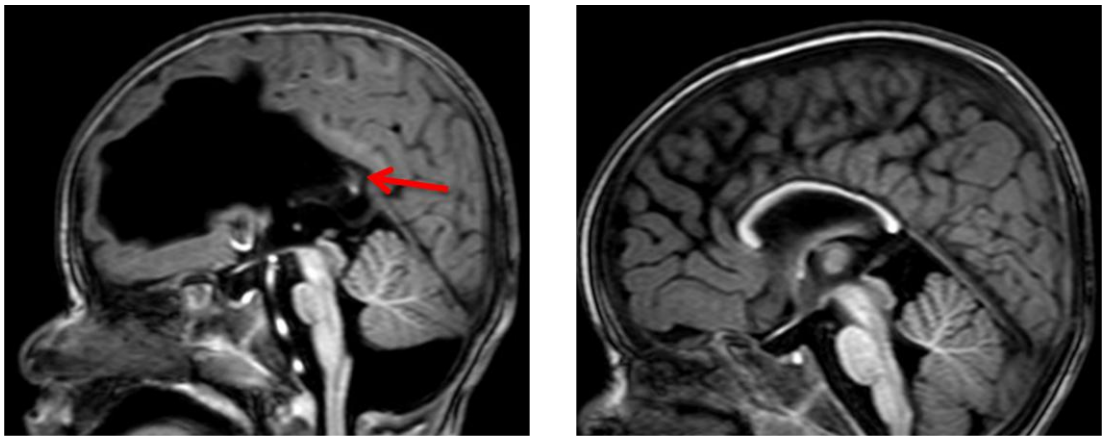


Figure – 26a: Case of grade 4 PVL with marked callosal thinning; only a small part of splenium is seen (arrow). **26b**: Another case of grade 3 PVL with diffuse callosal thinning

Table - 8: Shows the comparison of normal and thinned out frequencies and percentages of segments at midbody and splenium after Corpus callosal measurements

Thinning Status	**Midbody (Thickness/Length -0.072)**		**Splenium (Thickness/Length – 0.137)**	
	Frequency	Percent	Frequency	Percent
Absent	55	26.2	73	34.8
Present	149	71	131	62.4
Total	204	97.1	204	97.1
Data-N.A	6	2.9	6	2.9
Total	210	100.0	210	100.0

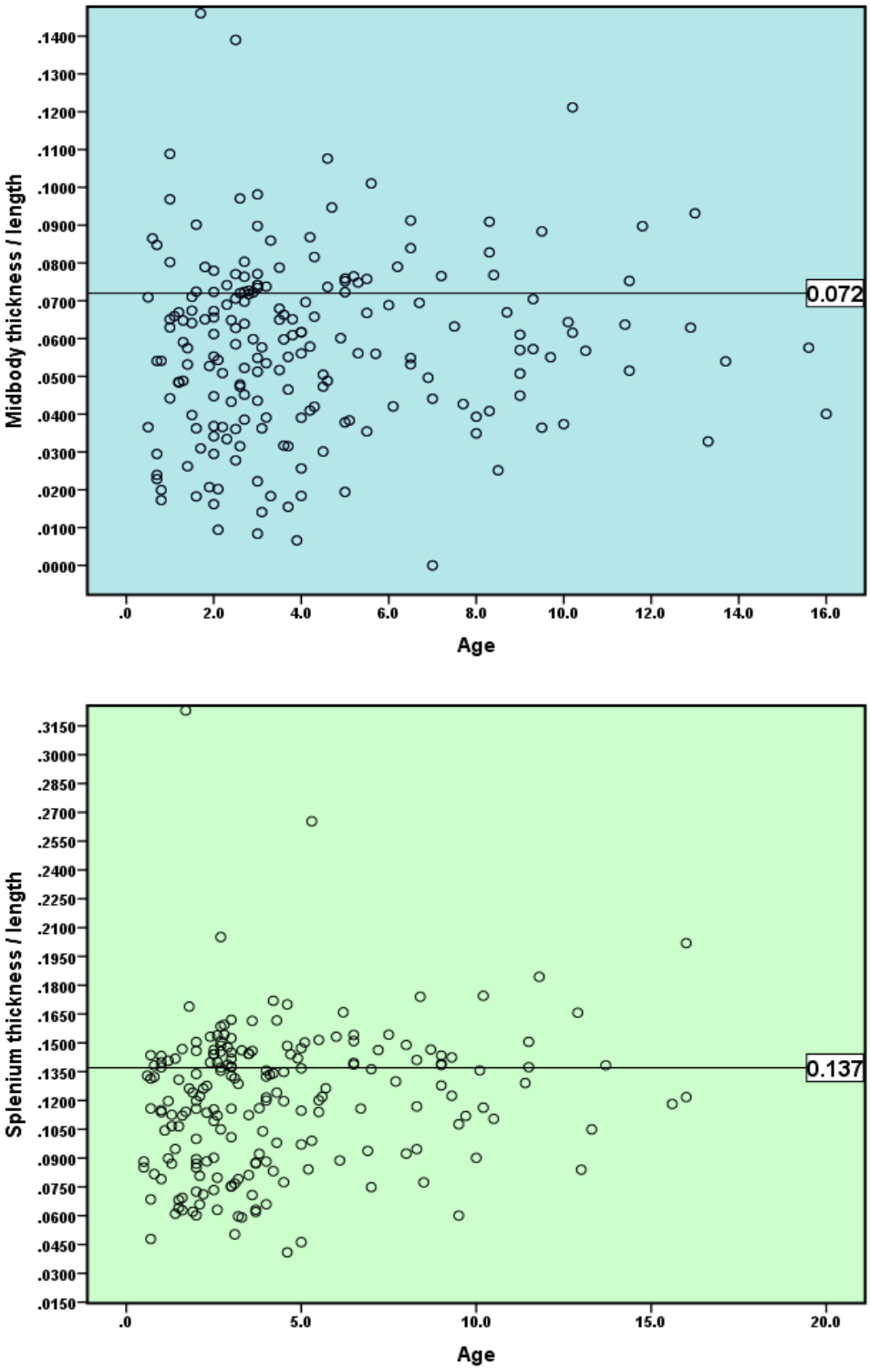


Figure -27: Scattered diagrams show the distribution of the values – ratio of the thickness to the length at midbody and splenium of corpus callosum. The dots below the reference line in each diagram indicate the cases with thinned out segments.

1) Correlation of callosal thinning with PVL

Table - 9: Cross tabulation of callosal thinning and PVL

PVL	Callosal thinning		Total
	No thinning	Thinning	
PVL absent	23	38	61
PVL present	12	130	142
Total	96	107	203

The table 9 gives the cross tabulation of corpus callosal thinning at any segment (midbody or splenium) with presence or absence of PVL. It was found to have significant statistical correlation with $p<0.001$.

2) Corpus callosal thinning in relation with grades of PVL:

The values obtained are shown in table 10, this reiterates a significant correlation between the degree of periventricular leukomalacia and corpus callosal thinning at midbody and splenium with $p<0.001$.

PVL Grades	Corpus callosal segments							
	Body				Splenium			
	Yes	%	No	%	Yes	%	No	%
Grade-0	29	47.5%	32	52.5%	23	37.7%	38	62.3%
Grade-1	12	75%	4	25%	6	37.5%	10	62.5%
Grade-2	45	73.8%	16	26.2%	41	67.2%	20	32.8%
Grade-3	43	95.6%	2	4.4%	41	91.1%	4	8.9%
Grade-4	20	100%	0	0%	20	100%	0	0%

Table no-10: PVL grades verses callosal segmental thinning

Figure 28 summarizes the percentage of corpus callosal thinning in various grades of PVL at midbody and splenium.

It was found that there was gradual increase in the prevalence of callosal segmental thinning as the grade of PVL progress. This had a significant statistical correlation with $p<0.001$.

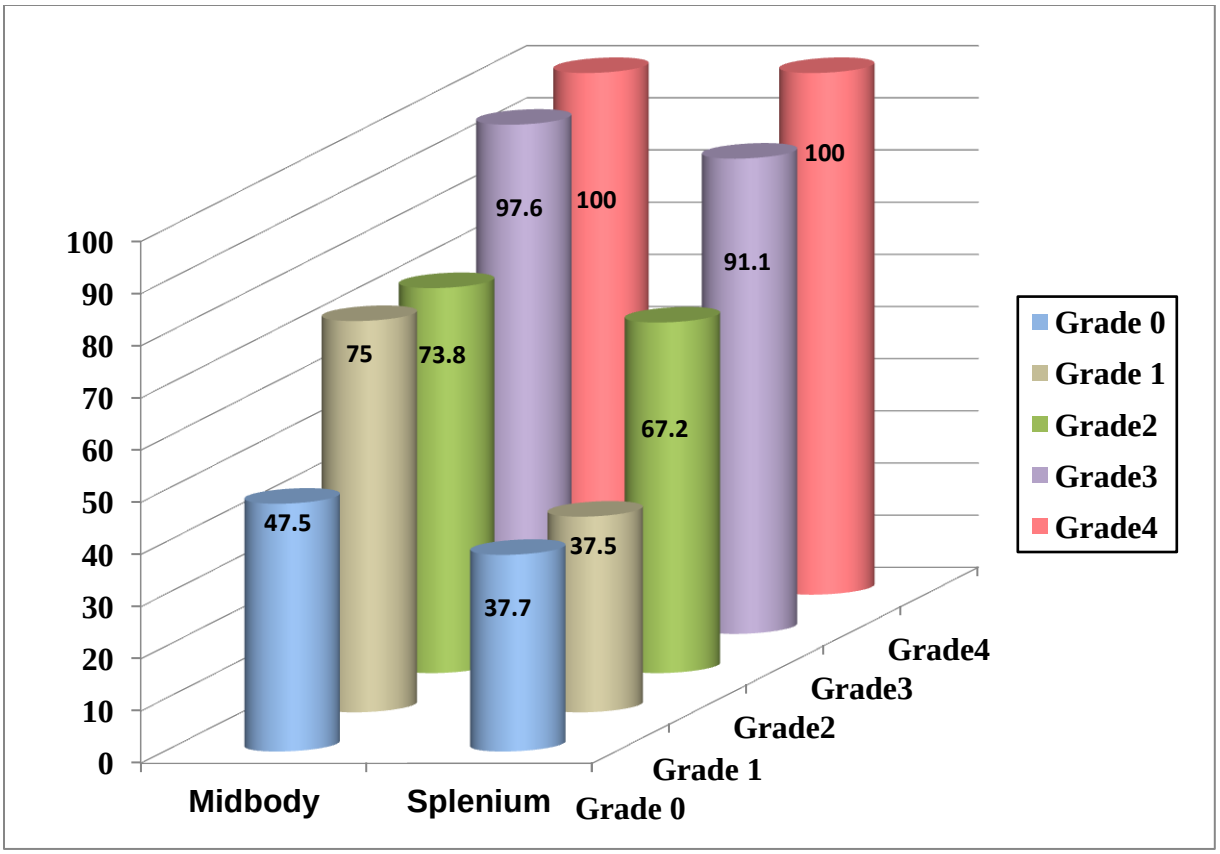


Figure – 28: Corpus callosal thinning in various grades of PVL at midbody and splenium

3) Corpus callosal thinning verses topography:

Quadriplegic CP group had more proportion of corpus callosal thinning. Extrapyramidal CP children had less involvement. The following tables 11 and 12 summarize the percentages of corpus callosal thinning in the 7 different types of topographies at midbody and splenium of corpus callosum respectively.

		Thinning of midbody		Total
		Normal	Thinning	
Topography	Diplegia	16	35	51
	Quadriplegia	3	42	45
	Triplegia	5	15	20
	Hemiplegia	3	26	29
	Monoplegia	0	1	1
	Extrapyramidal CP	14	12	26
	Mixed CP	11	14	25
Total		52	145	197

Table – 11: Corpus callosal thinning at midbody verses topography

		Thinning of splenium		Total
		Normal	Thinning	
Topography	Diplegia	14	37	51
	quadriplegia	7	38	45
	Triplegia	6	14	20
	Hemiplegia	12	17	29
	Monoplegia	0	1	1
	Extrapyramidal CP	20	6	26
	Mixed CP	9	16	25
Total		68	129	197

Table – 12: Corpus callosal thinning at splenium verses topography

DISCUSSION:

Epidemiology and risk factors:

This study is a hospital based study, which correlates the imaging findings on MRI brain of cerebral palsy children to the clinical profile, during the period Feb 2012 – October 2013.

1. Sex: In our study group 145 were male (69.05%) and 65 were female (30.05%). The male predominance is similar to the higher prevalence noted in the study from Banaras Hindu University, Varanasi, India in 2011(8) where they found 76.5 % CP children were boys. Male predominance in cerebral palsy is a known entity, and the same has been dealt in literature, with an average ratio of 1.9:1 (22,63,64). A referral bias is however possible which may contribute to the higher numbers among the males.

2. Gestational age: The larger proportion of preterm CP (31%) is indicative of the advancements in neonatal care in the country. The study which was done 11 years before in North India by Singhi et al. "clinical spectrum of cerebral palsy" (9) showed a very small proportion of pre-term (13.2%) CP children and is different from the statistics in our study.

Topography:

1. Topographically spastic diplegic CP (25.1%) is the most common type as seen from the various studies of developed countries and the recent Indian study (6–8). Spastic quadriplegic CP (24.1%) is the next common type which is followed by hemiplegic, extrapyramidal and

triplegic CP. An Indian study done in 2002, evaluating the clinical spectrum of CP in India(9) showed that quadriplegic CP (61%) group dominated, followed by diplegic (22%) and mixed CP(9); however the recent study done in Varanasi India(8) showed spastic diplegic CP (46.1%) as a dominant clinical spectrum. The current study shows higher proportion of spastic diplegia followed by spastic quadriplegia; however the difference is not statistically significant.

2. We found that diplegic CP is more commonly seen in the preterm infants although with no statistical significance ('p' measures 0.075). Previous studies have shown this association more significantly (3,65,66). Improvement in neonatal care of the preterm infants is probably contributing to the factor. Hence in future we may expect to see less number of cases diplegic CP in preterm children.

3. An interesting observation was the significant proportion of spastic triplegic topography (20 of 210) is 9.9%; this has not been identified previously in the major cerebral palsy studies mentioned (6–8). Asymmetric insults may also be seen in hypoxia and this could explain this topographical pattern.

MRI features correlation with perinatal clinical findings:

1. PVL:

1a. There is no statistically significant correlation between gestational age and prevalence of PVL in our study. PVL was conventionally thought a finding predominantly noticed in pre term infants due to ischemic injury. In our study we found that this is not true and PVL is seen equally in both term and pre term groups. ($p>0.05$). The other major causes of PVL are related to

infection due to premature rupture of membrane, unwarranted multiple pervaginal examination and chorioamnionitis (8). Pattern of blood vessel compromise theory may not be the only reason for PVL in Indian scenario (67).

1b. It is important to note that the same MRI features can present with different clinical picture. This may be important in the prognosis. It has been shown that PVL is more associated with cortical visual impairment. Therefore depending upon the MRI features more detailed evaluation and management strategy may be required which is not limited to motor rehabilitation. A specific study noted in our study, different to other studies is that periventricular white matter damage was present significantly in all clinical topographical patterns - quadriplegic (83.7%), diplegic (78.4%), hemiplegic (72.4%) and triplegic (70%) CP. So from the extent of white matter injury we cannot predict the clinical topographical pattern.

1c. Exposure to multiple risk factors in a single child could be the cause of overlapping of MRI features. We found that more than one MRI feature is seen in the same CP child.

1d. Quadriplegic CP children had the maximum number of grade 4 PVL (68). 16 (32.7%) out of 49 quadriplegic CP children had profound white matter damage and white matter volume loss, in which the gyri were virtually abutting the ventricles.

2. Deep gray nuclei involvement:

2a. Deep gray nuclei involvement was seen in equal proportion of preterm and term children in our study. Out of 37 preterm children who had deep gray nuclei involvement, 18 had history of neonatal hyperbilirubinemia. Profound asphyxia is also known to be associated with

deep gray nuclei injury in pre term children. Hence these perinatal insults explain the higher incidence of preterm involvement in our study.

2b. While isolated birth asphyxia or neonatal hyperbilirubinemia are not associated significantly with deep gray nuclei injury in our study, the combination of these two important risk factors has significant statistical correlation(p=0.006). This indicates that despite the advances and efforts to ensure optimal neonatal care, these still remain issues to be addressed in the developing countries which play vital role in deep gray nuclei injury. We had 114 children (54.3%) with deep gray nuclei injury, the second most common imaging abnormality found in our study, which is much higher than the only 12.8% reported in European cerebral palsy study. Hence, we have to conclude that in our country further attempts have to be made to reduce the occurrence of neonatal hyperbilirubinemia and birth asphyxia.

2c. Bilirubin encephalopathy (kernicterus) had a significant correlation in the etiology of extrapyramidal or dystonic cerebral palsy. (19 out of 27 dystonic CP) As described earlier this issue of high rate of bilirubin encephalopathy in the developing countries which can lead to deep gray nuclei injury and extrapyramidal CP. In our study there is statistically significant association between dystonic CP and neonatal hyperbilirubinemia (p = 0.002**).**

2d. Extrapyramidal or dystonic cerebral palsy is strongly associated with the deep gray nuclei injury which was seen in our study, 74.1 % of extrapyramidal CP children had deep gray nuclei involvement. Similar results were reported by Bax et al in the European CP study, in which it was found to be 76.5% (6). Since it is well known that bilirubin encephalopathy is associated with hearing impairment, in the children who have MRI features suggestive of

bilirubin encephalopathy like globus pallidus involvement, the child's hearing will also need to be evaluated clinically (69).

3. Perinatal stroke: Perinatal stroke is more commonly seen in term CP children. Perinatal stroke in the form of incomplete or complete arterial territory infarct was seen among the hemiparetic topographical group. 15 CP children on our study had features suggestive of perinatal stroke, 14 of these were term born. This correlates with literatures published till date, a strong link in the prevalence of perinatal stroke in term born children (70). Two of these 15 children had MR angiogram and both showed significant narrowing of the main artery of the involved territory and paucity of their branches.

The hemiplegic or hemiparetic CP group of children had mixed spectrum of MRI findings, thus no consensus pertaining to predilection can be obtained. The described pattern of involvement and clinical correlations noticed were similar to that reported in European CP study by Bax et al (6). Two other recently done studies (7,8) combined the perinatal strokes, deep gray nuclei involvement and cystic encephalomalacia as focal ischemic lesions, whereas in this study they have been dealt in isolation.

4. Cranial malformations: Intra cranial malformations generally presented as quadriplegic CP (48). In this study, of the 210 children only 7 (3.5%) had congenital malformation. In our study 5 children had quadriplegic CP out of 7 cases of malformation as described in literature. Of the other two children one child had vermian hypoplasia who presented as ataxic CP and the

other one had corpus callosal dysgenesis and craniovertebral junction anomaly who presented as spastic diplegic CP.

5. Perirolandic cortical gliosis: Perirolandic cortical gliosis is a common finding in term born and is uncommon in preterm children (2 out of 11). This is in keeping with the theory of vascular compromise in term asphyxia (38).

6. Miscellaneous MRI findings: Cerebellar atrophy had been seen among 5 children, of these 4 were term CP. Out of the 12 cases who had ulegyria 9 (75%) were term born. The other MRI features like hemiatrophy of cerebral hemisphere and Rasmussen encephalitis also noted and these features are suggestive of post infective or encephalitic sequel. One case of CMV infection with ocular, CNS, CVS and dermatological manifestation was also noted.

7. Normal MRI brain: The incidence of normal MRI brain study was only 4.8%, and 95.2% had abnormal MRI findings.

CORPUS CALLOSAL THINNING:

1. The correlation between the grades of PVL and corpus callosal thinning is significant with p value <0.001. A higher grade of PVL is associated with higher grade of thinning of corpus callosum. The only reference to date is the study done on only 43 spastic diplegic children which

has compared the grades of PVL with corpus callosal thinning at midbody and splenium (10). Our study has evaluated 210 children with CP under seven topographical patterns; our results are similar to the study mentioned above which showed significant correlation between PVL grades and the proportion of corpus callosal thinning at midbody and splenium. Grade 4 PVL is suggestive of profound white matter loss, and all these children showed marked callosal thinning.

2. Corpus callosal thinning is not significantly associated with any specific topographical pattern of clinical presentation ($p>0.05$). In all the topographic types, corpus callosal thinning was seen more frequently in quadriplegia (97.7%) followed by triplegic (90%), hemiplegic (89.7%) and diplegic (82.4%) topographic patterns.

3. While corpus callosal thinning is seen in extrapyramidal CP group as well, the degree of involvement is less (57.7%) as compared with the other topographical patterns.

4. Mid body segment is more commonly thinned than the splenium segment.

5. Corpus callosal thinning as an isolated finding is seen in 6 cases of clinically diagnosed CP. These cases are preliminarily reported as normal on routine reporting and only the calculation showed the abnormality. Out of the 16 normal MRIs we were able to find abnormalities in 6 (37.5%) and this helped in explaining the clinical condition of the child. Hence it is important to use callosal measurements and use them to calculate the ratio of thickness to length while reporting MRI of children with CP that may appear normal initially.

Limitation:

Although this being a tertiary referral centre, there is a small possibility, that the MRIs reviewed in this study, may not be representative of the entire spectrum of imaging in CP since this looks at only CP children who are brought to the hospital. There may be very severely affected children or children with minimal affectation who are not brought for various reasons.

We have conducted a cross sectional study with retrospective collection of clinical data.

Recent studies have included DTI and MRS in these patients. We have not included these indices as the information provided by these would be outside the aims and objectives and beyond the scope of our study.

CONCLUSION:

1. **(a) A set of specific MRI features can be seen in different clinical pictures.**

   (b) A particular clinical picture can have varied MRI findings.

   CP children with any particular topographical pattern of CP can have differing MRI findings.

   Hence, MRI is essential for deciding on management and counselling of such children and families.

2. **Normal MRI may be seen in a very small subset of patients with CP (4.8% in our study) even on 3T MRI.**

3. **PVL is the most common MRI abnormal finding in children with CP.**

   (a) The extent of PVL is not predictive of the clinical or topographic presentation of CP.

   (b) Higher grades of PVL are associated with higher degree of neurological deficit.

   For example grade 4 PVL has more cases of quadriplegic CP.

4. **Higher grades of PVL are associated with higher grades of thinning of corpus callosum**. Hence corpus callosal atrophy is very common in quadriplegic CP and relatively less seen in extrapyramidal CP.

5. **There is significant correlation between deep gray nuclei involvement with history of either neonatal hyperbilirubinemia, birth asphyxia or both.**

6. **Dystonic cerebral palsy is strongly associated with the deep gray nuclei involvement,** and kernicterus was found to be the main etiological factor.

7. **Perinatal strokes (arterial territory infarcts) are often seen in term CP.**

8. **Corpus callosal thinning was the only abnormal finding in 6 children with clinical CP.** Thus it is important to use corpus callosal measurements and compare with the normal standard ratio while reporting MRI of children with CP.

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Appendix – 1: ABSTRACT

TITLE OF THE ABSTRACT : MRI spectrum of cerebral palsy

OBJECTIVES: To describe MRI brain spectrum in a group of Cerebral Palsy children and correlate with perinatal history, clinical subgroups. To correlate callosal thinning with topographies and periventricular leukomalacia grades.

METHODS: IRB approved observational study (cross sectional study) on CP children in between the period March 2012-October 2013 in Christian Medical College, Vellore. The important MRI features described are periventricular leukomalacia (PVL), deep gray nuclei involvement, cystic encephalomalacia, arterial territory infarcts, corpus callosal thinning, perirolandic cortical gliosis and malformations. These were correlated with the relevant perinatal history and clinical subgroups by cross tabulation and Chi square tests.

RESULTS: A set of specific MRI features can be seen in different clinical pictures and a particular clinical picture can have varied MRI findings. Higher grades of PVL are associated with higher degree of neurological deficit and higher grades of thinning of corpus callosum. Deep gray nucleus signal abnormalities are seen significantly with combination of neonatal hyperbilirubinemia and birth asphyxia. Dystonic cerebral palsy is strongly associated with the deep gray nuclei involvement. Callosal thinning may be an isolated finding in CP.

Appendix – 2: Proforma

Spectrum of MRI features of cerebral palsy with relation to the clinical profile

serno - Serial number _____
hospno - Child's hosp number _____
name - Name of Child _____
age - Age of child ___ (in year)
sex - Sex ___ (1 - Male 2 - Female)
cons - Consanguinity ___ (0- not consanguine ; 1-consanguine)
del - Delivery ___ (1. Normal hospital, 2. Caesarean 3. Breech extraction 4. Instrumental 5. Home delivery)
wt - Birth weight ___ (in grams)
ga - Gestational age (weeks)

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pvl - Periventricluar leucomalacia ___ (0-not there;1-mild;2-moderate;3-severe;4-profound)
enceph - Multicystic encephalomalacia ___ (0-Absent; 1- cystic; 2- macrocystic)
Corpus callosum - measurement
whole length - len ___
genu - ___ cc thinning - genu ___ (0-normal; 1- thinned)
body - ___ cc1 thinning - midbody ___ 0-normal; 1- thinned)
spln - ___ cc2 thinning - splenium ___ (0-normal; 1- thinned)
dgn - Deep gray nuclei invol ___ (0- not involved; 1-early;2-late)
infar - Cortical infarct ___ (0-Absent; 1- Incomplete; 2- Complete)
malf – Malformation ___ (0-no; 1- yes)
cal - Periventricular calcification ___ (0-no; 1-yes)
bell - cerebellar atrophy ___ (0-no; 1-yes)
rol - Perirolandic cortex inv ___ (0-no; 1-yes)
any specific MRI feature ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

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topo - Topography ___ (1-Diplegia, 2-quadriplegia, 3-triplegia, 4-hemiplegia, 5-monoplegia, 6-EP CP(dystonic CP), 7-mixed)
tone - Tone ___ (1-spastic 2-dystonic 3-mixed 4-ataxic)
bil - Neonatal hyperbilirubinemia ___ (0-no; 1- yes)
ptm - preterm or term ___ (1-preterm;2-term;3-post dated)
ipcmp - Specific complication ___ (1-Meconium, 2-APH, 3-PIH, 4-prolonged labour, 5-Others)
torch - Congenital infections ___ (1-Toxo, 2-Rubella, 3-CMV, 4-Herpes)
cry - Cried after birth ___ (1-yes, 0-no)
seiz - Neonatal seizures ___ (0-no, 1-yes)
any other neonatal specific illness ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Appendix – 3

Information Brochure

Dear parents of ----------

Your child has been diagnosed to have brain problem and undergone a MRI scan as advised by the developmental pediatrician. We are going to conduct a research study by analyzing the MRI features of the children who have the same kind of problems like your child.

Purpose of study:

Aim of the study is to describe the MRI scan features of CP in Indian children with relation to the causes, pattern of involvement and functional classification. There are quiet few studies done on MRI scan features of CP in world, only one study so far done on Indian CP children. As per the clinical experience of our Indian pediatricians and the doctors from developmental pediatrics department of CMCH Vellore, Indian CP children are different from western CP children. Hence the MRI pattern also will differ. Hence we are going to analyze the MRI scan pattern of involvement in CP children.

Study conduct:

The child has been clinically evaluated by developmental pediatricians and sent for MRI scan brain after being clinically diagnosed as CP. Study starts after analyzing the MRI scan features. The MRI scan study will be reviewed by two radiologists separately. And the MRI abnormalities will be tabulated and analyzed with relation to the clinical data provided.

Benefit of the study:

We are hoping that this study will provide a framework for different image patterns of cerebral palsy in these children which can be adopted in other centres in India. We can find out the cause of cerebral palsy in some situation. MRI scan helps in predicting the probable course of illness in the coming years of the child.

CONSENT FORM

I, _____

(Printed name of parent / guardian signing the form)

- Confirm that I have read (or the information has to be read to me) and understood the written consent form for the parent / guardian for study. Study conduct and purpose has been explained to me.
- Confirm that I have been given enough time to consider the participation in the study, I have had the opportunity to ask question and I have been provided with satisfactory answers.

By signing the consent form I voluntarily agree to use my child's MRI scan data for this study purpose.

I understand that I can withdraw my consent at any time without having to give any reason. This will not have any impact on my child's right to receive the medical care he or she is entitled to.

Child's name: _____
Hospital number:_____
Signature or left thumb impression of the parent / guardian:
_____
Date:_____
(Note: Only the signature of the legal guardian is valid)

Person obtaining the consent:

Signature: _____
Date: _____

CMCH, Vellore.

DATA SHEET