

Magnetic Resonance Spectroscopy in Pediatric Neurology

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Abstract. In the last three decades a range of non-invasive biophysical techniques have been developed, of which Magnetic Resonance (MR) has proved to be the most versatile. Its non-invasive and safe nature has made it the most important diagnostic and research tool in clinical medicine. MR Spectroscopy (MRS) is the only technique in clinical medicine that provides non-invasive access to living chemistry *in situ*. This article focuses mainly on proton MRS in brain and also phosphorus MRS in calf muscle, with particular reference to the pediatric population, the normal spectrum and its use in various disease conditions in the practice of pediatric neurology. Few representative case studies among different disease groups have also been detailed. [Indian J Pediatr 2003; 70 (4) : 317-325]

Key words : Magnetic resonance imaging; Magnetic resonance Spectroscopy (MRS); Proton MRS; Phosphorus MRS

Physiological studies both under normal and pathological conditions have always been important to medical science. While studies under normal conditions are crucial for understanding the functioning of a system, those under pathological conditions are important for studying the mechanisms of disease in order to design appropriate treatments. Many major technological advances have been applied in biological and clinical research: the resulting improvements in instrumentation have helped in conducting more accurate and elegant experiments to enable the living system to be interrogated. Many metabolic studies to date, however, have been invasive to varying degrees. This implies that the metabolism is often disrupted during the process of extraction of the sample and consequently, the results may not be representative of the *in vivo* situation.

In the last three decades, however, a range of non-invasive biophysical techniques has been developed, of which Magnetic Resonance (MR) has proved to be the most versatile.¹ Its non-invasive and safe nature has made it the most important diagnostic and research tool in clinical medicine. In biological studies, MR imaging (MRI) is not a completely new technique since there are other imaging methods available. However, MR Spectroscopy (MRS) is the only technique in clinical medicine that provides non-invasive access to living chemistry *in situ*.

The technique of MR utilises the magnetic properties of atomic nuclei. The first MR experiments were conducted by the groups of Bloch and Purcell in 1946, for which they were jointly awarded the Nobel Prize in 1952. From being a method for measuring the magnetic

properties of atomic nuclei, MR has evolved into a powerful analytical tool in both laboratory and clinical settings. This has been made possible largely through the use of modern computer systems, combined with technical advances in magnet design. A variety of biological investigations have been carried out using MR, ranging from tissue metabolism, tissue characterization, blood flow and functional studies to drug binding studies in pharmaceutical research.

In the proton spectra from brain, metabolites such as N-acetylaspartate (NAA), Creatine/Phosphocreatine (Cr/PCr), Choline (Cho) containing compounds, glycine, glutamine, glutamate, taurine, aspartate, myo-inositol and alanine can be observed. While NAA is considered a neuronal marker, Cr/PCr is involved in high energy metabolism, and Cho is involved in membrane turnover. In pathology, increase or decrease of metabolites or presence of new metabolites are usually observed.

Although a number of nuclei can be studied using MR, proton is the most widely studied nucleus. This article focuses on proton MRS in brain, with particular reference to the pediatric population.

MRS can be useful in evaluation of ischemic penumbra of stroke, brain development (myelin and neuronal dysgenesis), head trauma (evaluation of cerebral damage not visible with MRI), degenerative disorders (identification of microscopic pathology not visible with MRI); and metabolic disease (metabolic disturbances with specific metabolic patterns).^{2,3} The differential diagnostic uses of metabolites of MRS is detailed in Table 1

Normal Finding in MRS

It is well known that MR imaging is highly sensitive in assessment of state of myelination during postnatal brain development.^{4,5} This seems to be true for proton MR

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spectroscopy also as there are striking differences in spectra with respect to a child's age. The volume localized spectra of white matter in healthy children are dominated by three prominent peaks from the methyl groups : NAA at 2 ppm, Cr / PCr at 3 ppm and Cho at 3.2 ppm.

Comparison of relative peak intensities of NAA, Cr/PCr and Cho during normal brain maturation reveals considerable changes in Ch and NAA. Whereas a spectrum in neonatal brain at the onset of myelination shows high signal intensity for the Cho containing

TABLE 1. Differential Diagnostic Uses of Metabolites in MRS^{2,3}

Metabolite (Normal cerebral concentration)	Characteristics	Decreased	Increased
1. Creatine (Cr) and phosphocreatine (PCr) (8mM)	a. Marker of intact brain metabolism. b. Biosynthesis in kidney and liver	<ul style="list-style-type: none"> • SIADH • Hypoxia • Stroke • Tumor • Trauma 	<ul style="list-style-type: none"> • Hyperosmolar increasing with age
2. Lactate (Lac) (~1mM : not visible because of its low concentration)	a. End product of anaerobic metabolism. b. Marker of ischemia c. Interruption of Krebs cycle and inhibition of pyruvate dehydrogenase increases brain lactate level	<ul style="list-style-type: none"> • Unknown 	<ul style="list-style-type: none"> • Hypoxia • Stroke • ICH • Hydrocephalus • Near drowning • Lymphoma • Tumor
3. MyoInositol (ml) (5mM)	a. Astrocyte marker b. Cell volume regulator c. Increase in osmotic stress of brain	<ul style="list-style-type: none"> • Stroke • Tumor • Hypoxia • Hyponatremia • SIADH 	<ul style="list-style-type: none"> • Neonates • Renal failure • Diabetes mellitus • Recovered hypoxia
4. N-Acetyl Aspartate (NAA) (8-9mm)	a. Most intense signal in normal brain. b. Normal NAA indicator of normal neuronal and mitochondrial function	<ul style="list-style-type: none"> • Hypoxia-Alexander • Infancy • Ischemia-herpes • Epilepsy • MS • Tumor • Trauma • Any degenerative disease 	<ul style="list-style-type: none"> • Canavan's • Axonal recovery (MELAS, MS) • Infant development
5. Choline (Cho) (1.5mM)	a. Membrane synthesis b. Membrane degradation is the main source c. Dietary and systemic sources diffuses freely into brain	<ul style="list-style-type: none"> • Hepatic encephalopathy • Stroke • SIADH • Cryptococcoma 	<ul style="list-style-type: none"> • Trauma • Tumor • Stroke (common) • Neonates
6. Lipids	a. Presence always pathological (contamination not considered) b. Indicative of severe pathological process liberating membrane lipids	<ul style="list-style-type: none"> • Not detectable 	<ul style="list-style-type: none"> • Contamination from outside volume e.g. scalp • Lymphoma • Necrotic area in tumor • Tuberculoma • Some type of Brain abscess • TOXO • Trauma
7. Glutamine (Gln) and Glutamate (Glu) (Gln approx 5mM, Glu approx 10 mM)	a. Astrocyte marker b. Increase in state with dystrocyte replacement of neurons c. These act as neurotoxins, inhibition of redox cycle leads to accumulation of lactate	<ul style="list-style-type: none"> • Trauma • SIADH • Hyponatremia 	<ul style="list-style-type: none"> • Acute hepatic encephalopathy • Hypoxia • Near drowning

ICH : Intracranial hemorrhage; MS : Multiple sclerosis; TOXO : Toxoplasmosis; MELAS : Myopathy, encephalopathy, lactic acidosis with stroke like episodes; SIADH : Syndrome of inappropriate antidiuretic hormone secretion

compounds and relatively low signal intensity for NAA, this pattern is reversed in children over one year of age, in whom myelination is complete. Other visible compounds are glutamate, glutamine glycine, taurine and inositol. These are seen depending on their concentration.⁶

Epilepsy

A decrease in level of NAA is helpful in accurate presurgical localization of epileptic focus³. MRS is useful in temporal lobe epilepsy prior to surgery. In mesial temporal sclerosis, there is a decrease in NAA signal from the affected temporal lobe. Gray matter heterotopias are found in 10% children with refractory seizure. These can be diagnosed by MRS.

Brain Tumors

Wang *et al* reported that for intraaxial tumors, lower NAA to choline ratios are associated with more aggressive tumor type.⁷ When discriminant analysis with NAA and Cr/ Pcr to Cho ratio is done. Diagnosis can be established with approximately 83% certainty for cerebellar tumor⁸. Pediatric cerebellar tumors are dominated by three major tumor types primitive neuroectodermal tumor, astrocytoma and ependymoma. Most primitive neuroectodermal tumors have low NAA/Cho and Cr / Pcr Cho ratio. The Cr/Pcr Cho ratio is higher in ependymoma than in astrocytoma. Preus MC *et al* (in society of magnetic resonance in medicine meeting, August 1994) reported that five major type of supratentorial tumor in adults can be distinguished by using in vivo proton MRS.⁹ Reduction or absence of NAA is seen in tumors derived from astrocytes like glioma, meningiomas and craniopharyngeoma. Lactate is seen in cystic areas and necrotic tissues.^{10,11}

There are five biochemical defects common to the majority of brain tumors, as measured by MRS. They are as follows : NAA is decreased; lactate is seen, lipid is seen (especially in areas of necrosis); creatine and phosphocreatine (PCr) is decreased; and choline is increased.

Neurocysticercosis (NCC)

Evaluation of inflammatory granulomas using MRS by Jayasundar R *et al* revealed an extremely low level of metabolites together with a poor signal/noise ratio in NCC. Lipids were seen in 86% of tuberculomas while in NCC and nonspecific inflammatory granuloma, lipids were seen in 20-21% cases.¹²

Intracranial Tuberculomas

Gupta *et al* reported the result of localized proton MR spectroscopy carried out on two patients with intracranial tuberculoma.¹³ A large resonance was observed between 0.7 and 1.6 ppm which was assigned to (CH₂) group of saturated fatty acids. This peak was attributed to large lipid fraction present in tubercle bacilli. Distinct resonances of serine and phenolic lipids were seen in ex vivo and in vitro studies of tuberculous granuloma. The

lipid extract of granuloma and mycobacterium tuberculosis showed phenolic lipids at 7.1 and 7.4 ppm, a constituent of cell wall of the bacteria in a tuberculoma. From these studies, it is clear that intracranial tuberculomas are characterized by a spectral pattern that involves primarily lipid resonance. Jayasundar *et al* have also reported the predominant occurrence of the lipid resonances in tuberculomas.^{12,13}

Brain Abscess

Kim *et al* performed MR spectroscopy in seven patients with pyogenic brain abscess and in seven patients with necrotic or cystic brain tumor. Six of seven patients with abscess showed resonance from lactate, valine, alanine, leucine, acetate succinate and unidentified metabolites (2.2, 2.9, 3.2, 3.4, and 3.8 ppm). In contrast, six of seven patients with tumor showed only a resonance attributed to lactate. Dev *et al* used localized MR spectroscopy on 24 patients with pyogenic brain abscess. Post aspiration studies were performed for 12 patients treated with combined medical and surgical therapy and 2 patients treated medically. Lactate and amino acid were seen in all of the spectra for all patients, regardless of time of spectroscopy after the onset of combined medical and surgical therapy. Acetate and pyruvate disappeared after 1 week of combined therapy. Grand *et al* suggested that the presence of amino acid resonance could provide a means for identifying abscesses and distinguishing these masses from necrotic region of brain tumor.¹³

Head Trauma

MR spectroscopy provides a way to evaluate tissue viability and to characterize the metabolic disorders associated with each type of injury. Result of MR spectroscopy may provide insight as to how patients should be treated and whether treatment is effective, thus helping neurosurgeons make clinical decision. Wan *et al* demonstrate that the injured region had highly increased lactate signal (Lactate / creatine = 0.8 approximately, three to five times normal) and decreased NAA (NAA_i/NAA_c = 0.26), creatine (creatine_i / creatine_c = 0.25) and choline (choline_i/choline_c = 0.2 signals (subscripts 'i' and 'c' denotes signals from injured and control region respectively. Increase in lactate is related to tissue swelling and ischemia after trauma, and decrease of choline, creatine and NAA is related to edema, which has a dilution effect.^{9,13}

Stroke

MR spectrum in areas of stroke and in diseases like sickle cell disease or MELAS shows an elevated lactate even before neuroimaging can pick up these abnormal areas. Areas of transient ischemic attack may show decrease in NAA/ Cr ratio but, lactate is not detected. Follow up MRS studies show a return of NAA level to normal indicating the recovery of partial neuronal injury.⁷

Reff Syndrome (RS) and Autism

Hashimoto *et al* performed proton MRS of the brain in 3 cases of RS in comparison with autism and controls. RS is a clinically defined disorder characterized by autistic behaviour and cognitive and motor skill loss early in life. The older patient with RS demonstrated decreased NAA/Cho and NAA/Cr ratio when compared with the autism and control groups, whereas the younger patients did not demonstrate these decreased metabolite ratios. This data suggest that there may be a secondary degenerative process of late onset RS which is pathophysiologically different from autism.^{15,16}

Pelizaeus-Merzbacher disease

Pelizaeus-Merzbacher disease is a rare myelination disorder with muscular hypotonia, psychomotor retardation and ocular nystagmus.¹⁷ The basic defect is an X-linked recessive disorder with loss of myelin due to an in born abnormality of proteolipid protein, a major protein component of myelin. MR spectroscopy in this case revealed drastically diminished NAA and elevated choline in affected cerebellar white matter.⁶

Canavan's Disease

Canavan's disease is an inborn error of metabolism characterized by aspartoacylase deficiency with cystic degeneration of oligodendroglia and astrocyte swelling. The patients present with megalencephaly, blindness, spasticity and psychomotor retardation. Aydinli *et al* demonstrated elevated levels of N-acetylaspartate (NAA) compare to choline and creatine in the frontal region white matter. MRS from areas of demyelination demonstrate increase in NAA/Cho ratio, this is not only due to reduction of choline containing compound in brain but also due to increase of NAA concentration. The in vivo measurement of NAA, choline and creatine in the brain by MRS offers an additional non invasive diagnostic test for establishing the diagnosis of Canavan's disease. CSF, plasma and urine also shows high level of NAA due to deficiency of aspartoacylase.^{18,19}

Metachromatic Leukodystrophy (MLD)

MLD is an autosomal of recessive lysosomal storage disease caused by deficiency of lysosomal activity of arylsulatase A, which results in an accumulation of sulfated lipids in myelin sheath in both peripheral and central nervous system. The late infantile form is characterized by loss of motor and cognitive skills behaviour problems starting before 4 years progressing to death. Proton MRS revealed a marked reduction of neuronal marker NAA in affected white and gray matter and elevated lactate in demyelinated areas in contrast to other Leucodystrophies MLO patients who showed a generalized increase of brain myo-inositol (2-to-3 fold in white matter), indicating a specific role in the pathophysiology of demyelination of MLD.^{20,21,22}

Adrenoleukodystrophy (ALD)

Childhood ALD is an X-linked disorder with a defect in peroxisome that involves impaired function of single specific enzyme (Lignoceryl-coenzyme A ligase). This defect leads to accumulation of very-long chain fatty acids (VLCFA) in central nervous system, adrenal cortex and testes. Neurological symptoms include attention disorder, seizures, visual and auditory disturbances progressively leading to vegetative state and eventual death. Tzika *et al* reported that MRS from white matter lesion showed 65% reduction in the ratio of NAA/ tCr; 55% increase in the ratio of choline-containing compounds (Cho) to tCr, 94% increase in ratio of glutamate, glutamine or inositol to tCr and lactate accumulation.²³

Alexander Disease

Alexander disease is a leukodystrophy characterized by presence of numerous Rosenthal fibers (RFs) i.e. inclusion bodies in astrocyte. The clinical manifestation includes psychomotor deterioration and megalencephaly. Elevation of α , β -crystallin and head shock protein 27 (HSP 27) in CSF and frontal dominant leukodystrophy is diagnostic. Takanashi *et al* demonstrated decrease in NAA with a lactate peak in frontal region but a normal NAA level without a lactic peak in posterior region.²⁴

Megalencephalic Leukoencephalopathy with Subcortical Cysts/Van der Knaap

Vacuolating megalencephalic leukoencephalopathy (VML) with subcortical cysts is a neurodegenerative disorder clinically characterized by megalencephaly with onset in the first year of life, progressive ataxia, spasticity and relatively spared cognitive function. Conventional MRI findings consist of diffusely abnormal cerebral white matter with subcortical cysts. Recent single-voxel proton MR spectroscopy studies have shown mild metabolic abnormalities in the white matter. 1H-MRSI examinations, which can provide simultaneously metabolic information from many different brain regions, showed inhomogeneous decreases in all normally detected metabolites with significant widespread decreases in the ratio of N-acetylaspartate to creatine+phosphocreatine and concomitant small increases in lactate in the white matter of both hemispheres. Metabolic abnormalities were milder in the frontal white matter and more severe in the posterior white matter. The 1H-MRSI pattern of the gray matter was normal in both patients.²⁵

Mitochondrial Disorders

Leigh Disease (Subacute Necrotizing Encephalomyelopathy)

Leigh disease is a recessively inherited familial disorder of infancy and childhood with variable clinical expression. This disease is caused by one of the several possible deficiencies that affect the oxidation of pyruvate, resulting in abnormally elevated levels of pyruvate and lactate.

Laboratory finding includes metabolic acidosis with elevated lactate and pyruvate concentration in blood and CSF. Characteristic necrosis are found in spinal cord, brain stem, and basal ganglia, especially putamen. MRS reveals elevated levels of lactate in the head of nucleus caudatus. The levels of NAA are low in areas of stroke associated with neuronal loss. MRS is also useful in assessing Leigh disease and in monitoring its treatment. Because at times blood and CSF lactate level do not reflect the brain lactate level. MRS is the most reliable method to monitor lactic acidosis in the brain. MRS can even detect areas of early ischemic changes earlier than MRI.^{6,9}

MELAS (Myopathy, Encephalopathy Lactic Acidosis with Stroke like lesion)

MRS can detect area of poor perfusion and stroke earlier than other neuroimaging modalities. These areas show elevated levels of lactate. Successful treatment with sodium dichloroacetate and improvement in perfusion lead to reduction in lactate/creatine ratio. The decrease in NAA in area of hypoperfusion may return back to normal on reperfusion indicating reversible damage.^{6,9}

Attention – Deficit-Hyperactivity Disorder (ADHD)

Toft PB indicated a particular vulnerability to hypoxic injury of striatal neurons in the developing brain. Striatum is important for context recognition and behaviour. An elevation of lactate in striatum a part of frontostriatal circuit, which plays a vital role in human behaviour in neonatal period following adverse perinatal events like asphyxia, germinal matrix hemorrhage and intrauterine growth retardation may play important role in development of ADHD in later life.²⁶

Dyslexia

Dyslexia is characterized by language disorder in which reading ability is compromised because of poor phonologic skills. MRS in these patients revealed a difference in spectrum between them and normal control subjects in the temporo-parietal lobe. The cerebellum is also, biochemically, assymetrical on MRS in dyslexic men suggesting altered development of this organ. Instructional intervention therapy that improved phonological performance in dyslexic boys was associated with low levels of lactate in left anterior quadrand of brain compared to untreated patients.^{27,28}

Tuberous Sclerosis

MRS spectroscopy of tubers in patients with tuberous sclerosis revealed significant increase in myoinositol/creatine ratios in the tubers. The NAA/creatine /Pcr ratios in the tubers showed a significant decrease, and was considered to reflect a reduction of cranial neurons. The increase in myoinositol/creatine/Pcr ratio in tubers was considered to be a reflection of increase in glial tissue.²⁹

Hepatic Encephalopathy

Proton MRS in hepatic encephalopathy shows an elevation of Glutamine levels and a reduction in choline, myoinositol levels. A decrease in levels of myoinositol is seen in patients even with overt neurological impairment, therefore it is possible to screen for subclinical hepatic encephalopathy with MRS.

Friedreich Ataxia

Friedreich's ataxia (FA) is the most common form of autosomal recessive spinocerebellar ataxia and is often associated with a cardiomyopathy. The disease is caused by an expanded intronic GAA repeat, which results in deficiency of a mitochondrial protein called frataxin. ³¹ P nuclear MRS has shown that these patients have lower rates of mitochondrial ATP production in skeletal muscles than controls. This can be used to see response of newer possible therapeutic modalities.³⁰

Case Studies

1. K, a 13-year-old girl presented with right focal seizures with secondary generalization from the age of 10 years. She had multiple ring lesions on CT scan of head. Besides anticonvulsants she was given 2 courses of albendazole therapy and one course of praziquantel therapy. In left parietal region a lesion persisted for over 1 year for which MRI and MRS were done (Fig. 1a, 1b). This was suggestive of neurocysticercosis which can be easily distinguished from a tuberculoma (Fig. 2a, 2b)
2. A, an 8-year-old boy presented with progressively diminishing vision for 6 months and regression of motor milestones. His head circumference was normal, pupils normal size and normally reacting to light, generalized hypertonia and brisk reflexes. His MRI showed bilateral symmetrical changes in posterior parieto-occipital white matter. His Aryl sulfatase was normal but very long chain fatty acids were increased (Amount of C 26:0 and the ratios of C 24/22 and C 26/22 were higher than normal). Results were consistent with X linked adrenoleukodystrophy. His MRI and MRS findings are depicted in Fig. 3a, 3b. The spectrum from occipital lobe shows low level of Cr and Cho and drastic decrease in NAA though in literature high Cho and lactate have also been reported. The decrease in NAA in ALD is more than observed in other leukodystrophies.
3. Am, a 6-year-old boy presented with progressively increasing difficulty in walking for 2.5 years, generalized seizures and a progressively increasing large head size. His head circumference was 58 cm and had mild hypertonia bilateral lower limbs with brisk reflexes. His MRI showed extensive white matter hyperintensities scattered symmetrically bilaterally throughout the white matter. These

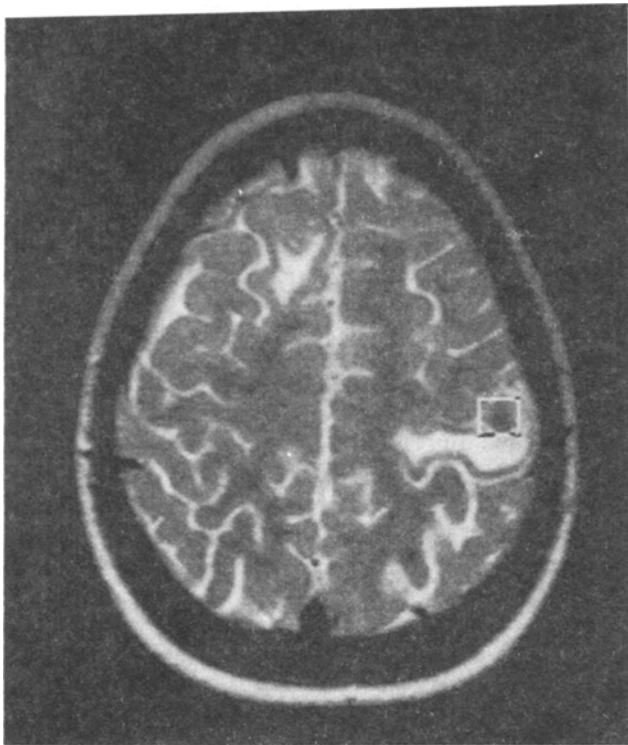


Fig. 1a

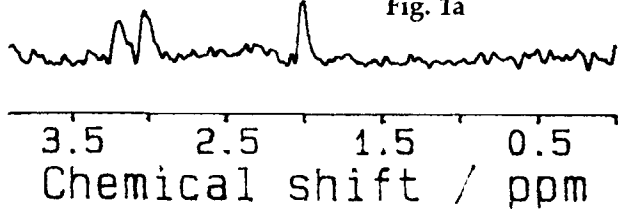


Fig. 1b

Fig. 1(a). T2 weighted MRI image from a child with persistent Neurocysticercosis. (b) The proton spectrum shows reduced levels of NAA, Cr and Cho. The peak observed at 2.00 ppm is identified as N-acetyl aspartate (NAA), at 3.00ppm Creatine / Phosphocreatine (Cr) and 3.2 ppm Choline (Cho).

involved the subcortical white matter as well as the periventricular region. The changes were more marked in the frontal, temporal and parietal region. Subcortical cysts were also present. His aryl sulfatase and very long chain fatty acids were normal. A diagnosis of Van der Knaap or Megalencephalic leukoencephalopathy with subcortical cysts was made. His MRI and MRS are depicted in Fig 4a, 4b.

4. BK, a 12-year-old child presented with progressively worsening ataxia since the age of 5 years, scoliosis, no telangiectasia, bilateral upgoing plantars, just elicitable ankle jerks and a negative Romberg. He had no recurrent sinopulmonary infections. Nerve conduction velocity showed peripheral neuropathy. A diagnosis of Friedreich's ataxia was made. His MRS of calf muscle before and

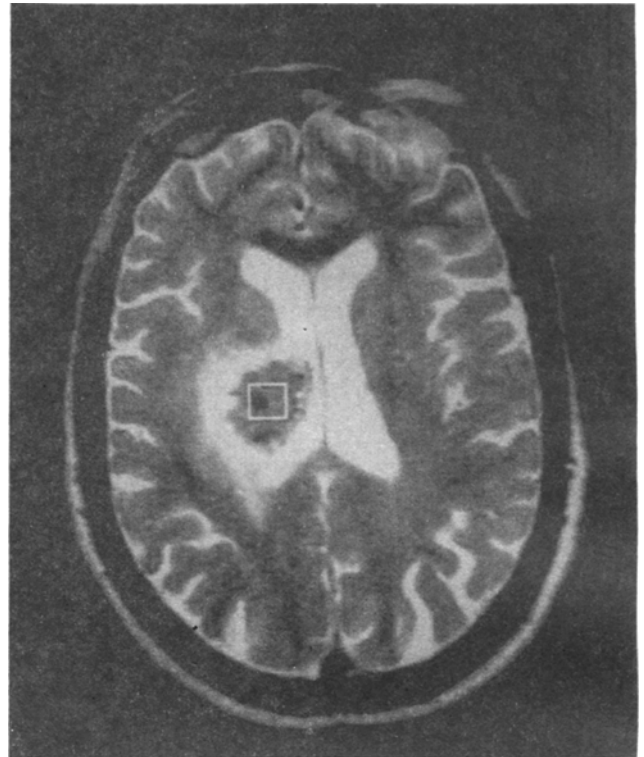


Fig. 2a

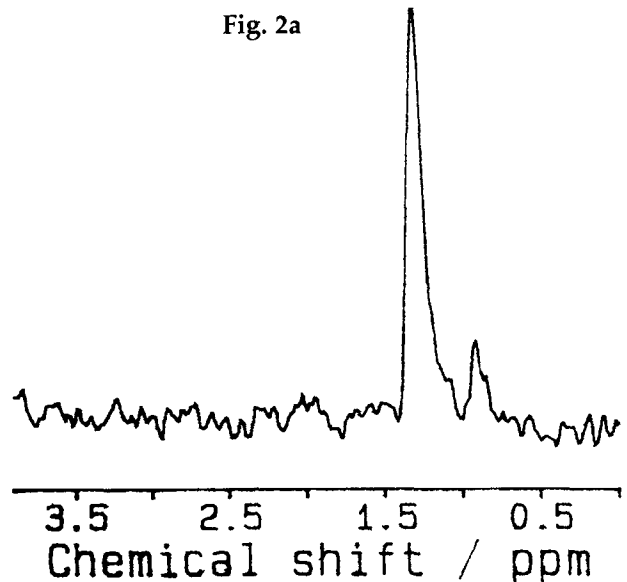


Fig. 2b

Fig. 2 (a). T2 weighted MRI image from a child with Tuberculoma. (b) The proton spectrum shows a huge lipid peak with no signal from NAA, Cr and Cho.

- after 6 months of treatment with thiamine and amantadine hydrochloride is shown in Fig 5a, 5b. There was no improvement on treatment.
5. RJ, a 10-year-old boy presented with hyperactivity and normal IQ. He had combined type of ADHD with significant inattention, hyperactivity and

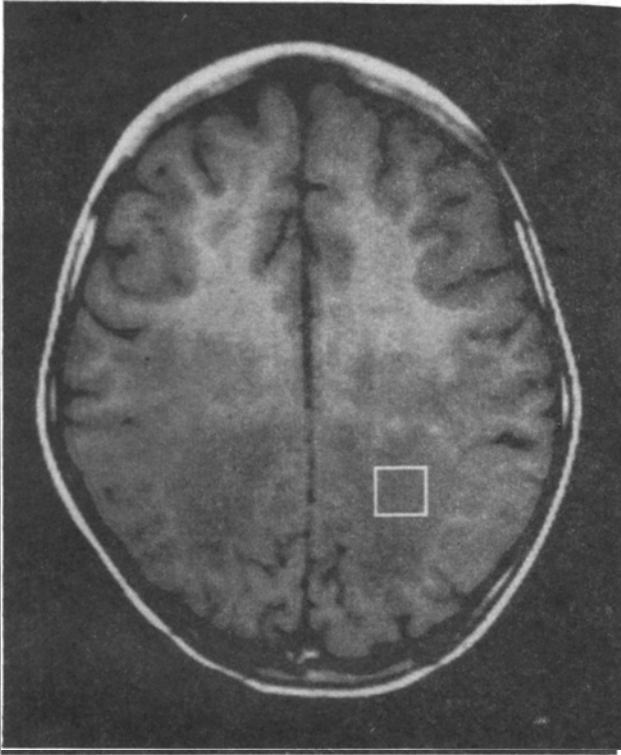


Fig. 3a

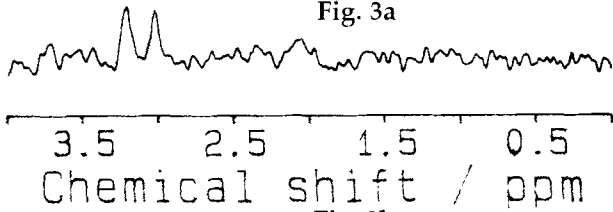


Fig. 3b

Fig. 3 (a). T1 weighted MRI image from a left occipital lobe in a child with Adrenoleukodystrophy. (b) The proton spectrum shows low level of Cr and Cho and drastic decrease in NAA. The decrease in NAA in ALD is more than observed in other leukodystrophies.

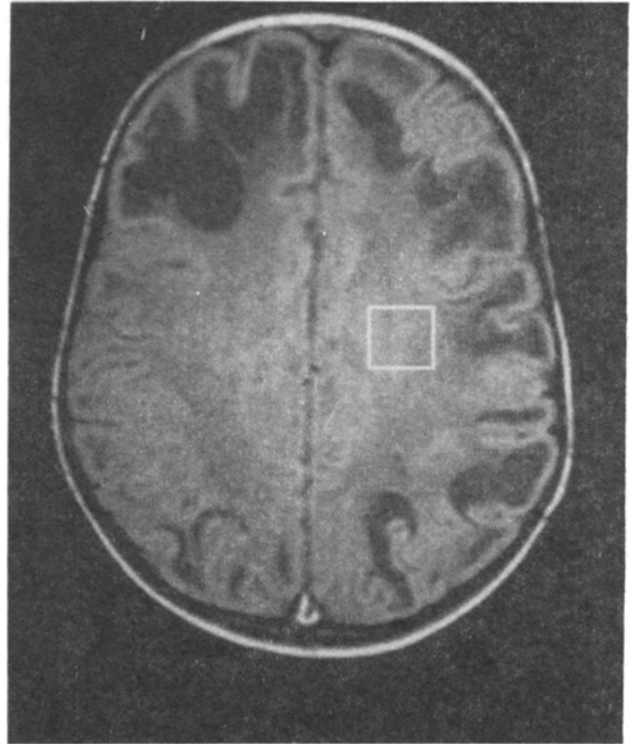


Fig. 4a

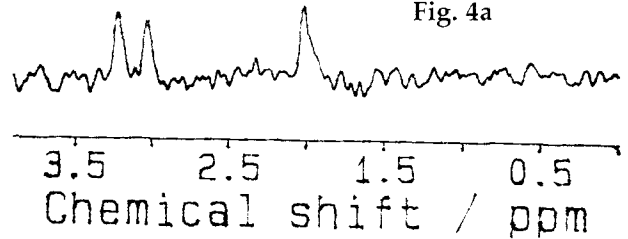


Fig. 4b

Fig. 4 (a). T1 weighted MRI image from a left parietal lobe in a child with Van der Knaap or megalencephalic leukoencephalopathy with subcortical cysts. (b) the proton spectrum shows reduced level of all metabolites.

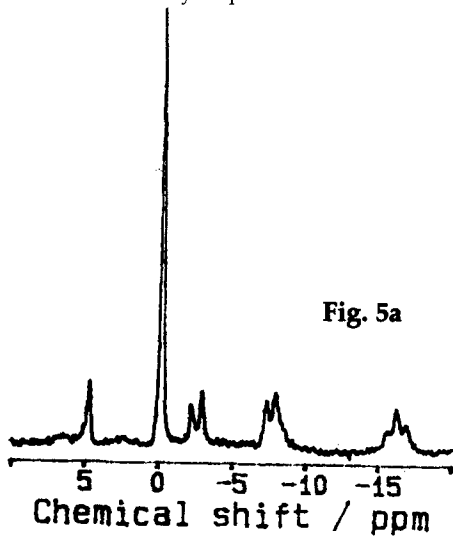


Fig. 5a

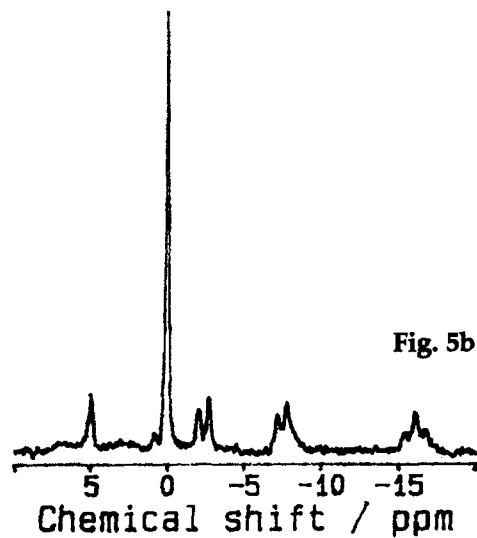


Fig. 5b

Fig. 5. Phosphorus spectrum from calf muscle from a child with Friedrich's ataxia (a) Pretreatment (b) Post treatment follow up. The spectrum identifies prominent phosphocreatine, with β ATP, γ ATP, α ATP inorganic phosphate.

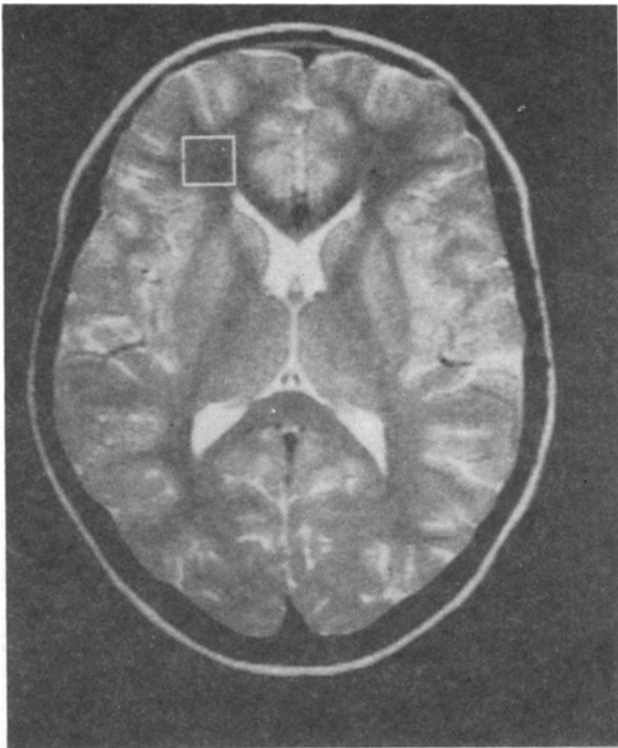


Fig. 6a

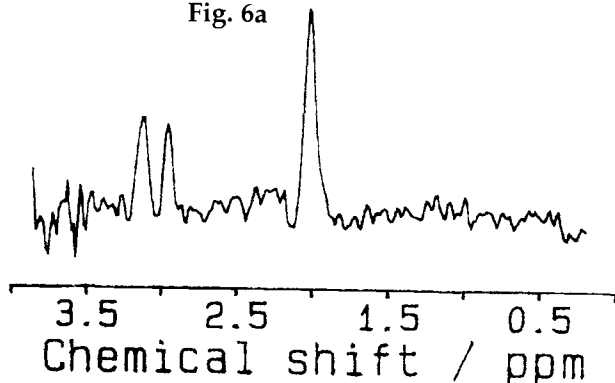


Fig. 6c

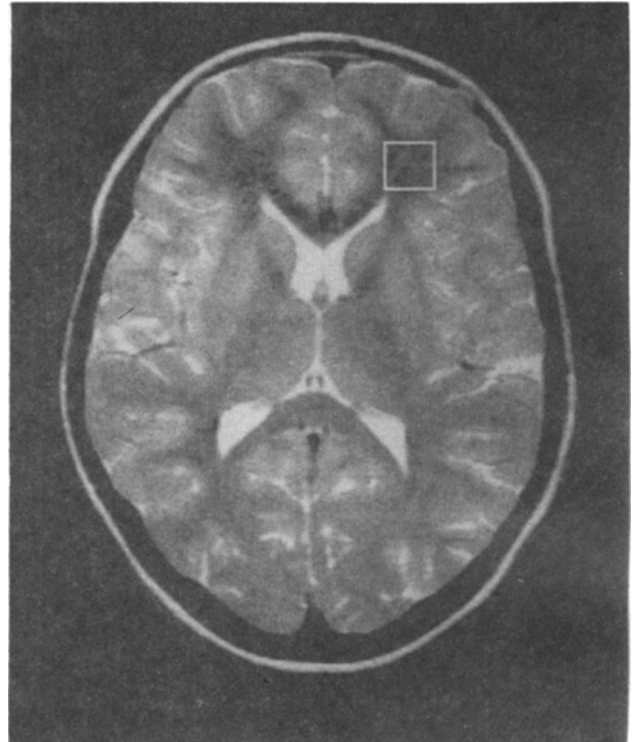


Fig. 6b

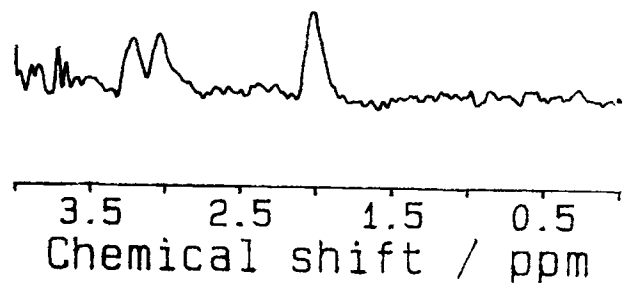


Fig. 6d

Fig. 6. T2 weighted MRI image from a (a) right prefrontal cortex (b) left prefrontal cortex from a child with Attention Deficit Hyperactivity Disorder. The proton spectrum acquired from right frontal lobe (c) is normal but abnormal spectrum with reduced metabolites level observed in the left frontal lobe (d).

impulsivity diagnosed by DSM IV criteria. His Single photon Emission Computed Tomography (SPECT) showed left basifrontal hypoperfusion. His MRI and MRS are depicted in Fig. 6a-d.

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Contributors

VK and SG were pediatric neurologists incharge of the cases, SG and SM drafted the manuscript, VK critically reviewed the manuscript and will act as guarantor for the paper, TS performed the MRS in all patients and RJ critically reviewed the manuscript