Review

Radiology

The Role of Radio-diagnosis in Inborn Errors of Metabolism

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ABSTRACT

Inborn Errors of Metabolism take a heavy toll of the patient as well as their relatives due to delayed diagnosis. These occur due to defective genes leading to various metabolic abnormalities. As genetic problems are countless, so are their manifestations. Timely identification of the disease entity is the key at least to a satisfactory, if not a complete successful management in many instances. Modes of presentation and clinical features are not always characteristic and have resemblance to routine day to day illnesses.

In this chaos, an appropriate use of modern strides in Imaging Sciences often enable to raise a strong suspicion in majority of the cases and even to confirm the clinical suspicion in some cases of inborn errors of metabolism. Not all of the medical fraternity is aware of this important role that radio-imaging can play. Hence a timely review of the Role of Radio-diagnosis in Inborn Errors of Metabolism is a must and is therefore attempted in this article. The author attempts to solve this diagnostic dilemma by discussing the role that each imaging modality can play to arrive at a final diagnosis. Multiple examples and images have been used generously to emphasize this point.

Key Words: Inborn errors of metabolism, Radiograph, Ultrasound, CT scan, MRI, MR Spectroscopy

KEY MESSAGE

- Recent advances in Radio-diagnostic Imaging Sciences have enabled us to diagnose inborn errors of metabolism, not only during the intra-uterine state in high risk cases with known family history but also immediately after birth even before the clinical manifestations begin in unsuspected cases. Moreover giant strides in imaging are also throwing light on inborn errors of metabolism as the underlying cause of unexplained deaths by showing new ways of performing MR Spectroscopy based 'Chemical Autopsy' in cases where conventional disfiguring autopsy is rejected by the parents. No one can debate that conventional autopsy or necropsy remains the gold standard in unexplained deaths, but the high acceptance of virtuopsy (performed using CT scan or MRI) makes it an acceptable alternative when the former is declined.

INTRODUCTION

The term – 'Inborn Errors of Metabolism (IEM)', encompasses a plethora of metabolic abnormalities which result from gene related problems. A defective gene causes reduced or almost no formation of enzymes that are necessary for the normal functioning of various metabolic pathways, in such a way that the toxic substance starts accumulating in an abnormal amount to cause damage to various systems in the body in one form or the other.

LITERATURE REVIEW

Archibald Garrod originally put forth the hypothesis of one gene-one enzyme and first used the term 'Inborn Error of Metabolism' for these inherited genetic, congenital disorders [1].

These disorders are broadly classified [1], depending upon the metabolic pathways which they affect the most. e.g. disorders of carbohydrate metabolism (e.g., glycogen storage disease), disorders of amino acid metabolism (e.g. phenylketonuria), disorders of organic acid metabolism (e.g. alkaptonuria) etc.

More than 500 types of these disorders have now been known to occur in humans [2]. Although the isolated cases are rare, the combined data is staggering in terms of their effect on the childhood health statistics. Hence, an early diagnosis is the need of hour, to ensure a better quality of life.

In British Columbia [1], the overall incidence was estimated to be 70 per 100,000 live births. In India, the exact burden of these metabolic abnormalities is still unknown, as there are no surveys which have targetted this specific question. However, the data [3,4] suggest that out of the 25 million annual births in India; 8 lakhs suffer from congenital malformation; 3.5 lakhs from glucose 6 phosphate deficiency (G6PD); 25,000 from metabolic disorders; 20,000 from Down`s Syndrome, 15,000 from congenital hypothyroidism, 14,000 from thalassaaemias and 5,000 from sickle cell anaemias. When 4400 patients who were suffering from mental retardation were biochemically screened, it was found that 256 cases (5.75%) were caused by various inherited metabolic disorders.

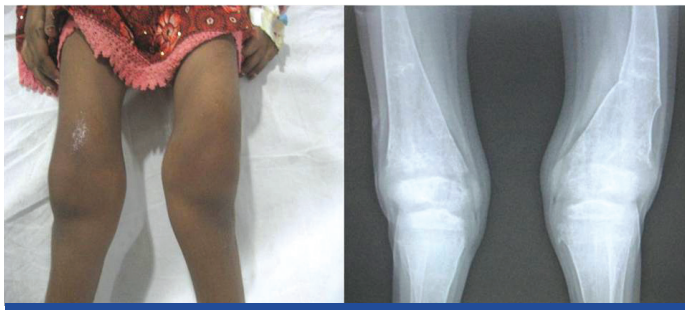
Due to the myriad forms of these diseases, the patients present to the clinics with countless types of manifestations [5]. The signs and symptoms are usually very non specific, like nausea, vomiting, failure to thrive and so on. Sometimes seizures and abnormal movements may also be seen.

Hence many times, when unsuspected patients are referred for various radiological examinations, certain characteristic radiological findings may be the first to raise a strong suspicion of the metabolic abnormalities and at times, may even be conclusive.

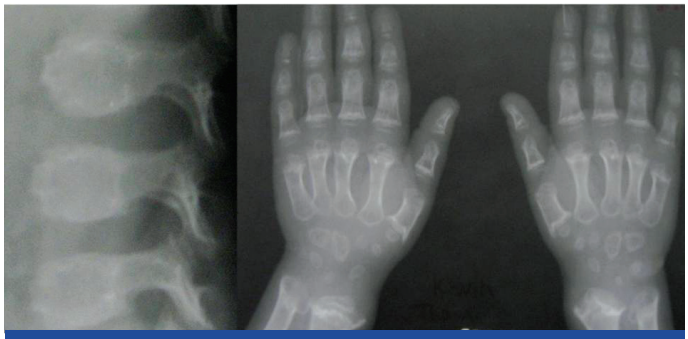
ROLE OF RADIO-DIAGNOSIS

1. **Plain Radiographs:** They are ordered as a routine workup for evaluating a sick child. Specific radiographs of certain body parts may be asked for, when such parts are affected and the results may even change the overall diagnosis. Here are a few examples.

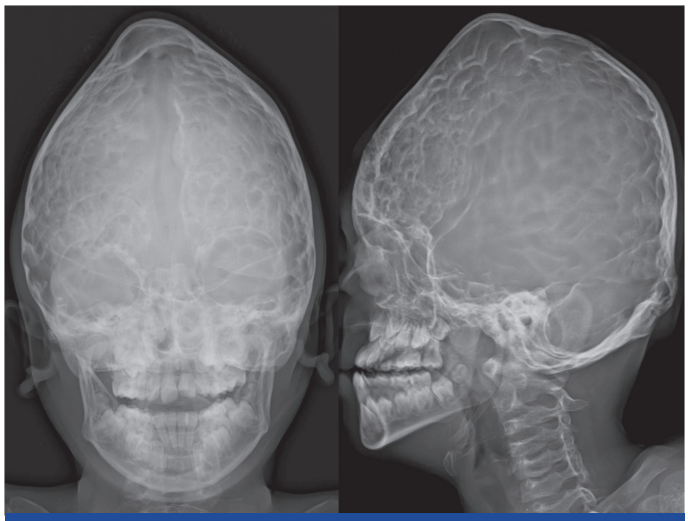
    a. A plain radiograph of the knees, when it was asked for in a sick child with knee swelling [Table/Fig-1], showed features which were typical of rickets and indicated an improper vitamin D metabolism. It thereby aided in diagnosing an inborn error of metabolism in this unsuspected patient.



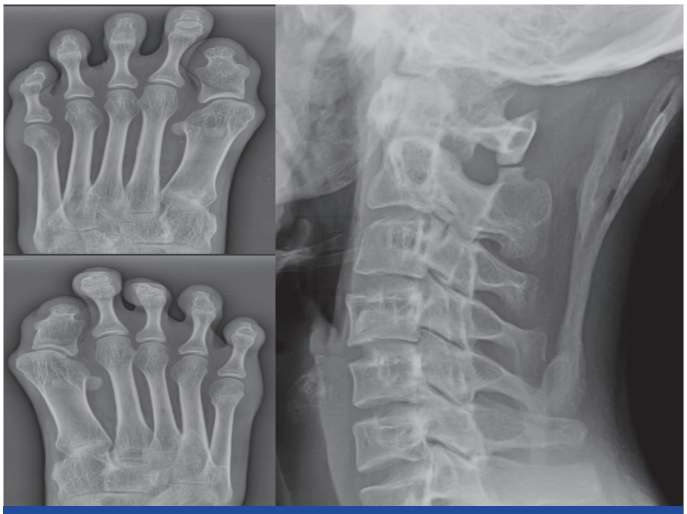
[Table/Fig-1]: Photograph of swollen knees and Plain radiograph of knees – AP View showing reduced bone density, demineralization, metaphyseal changes typical of rickets.



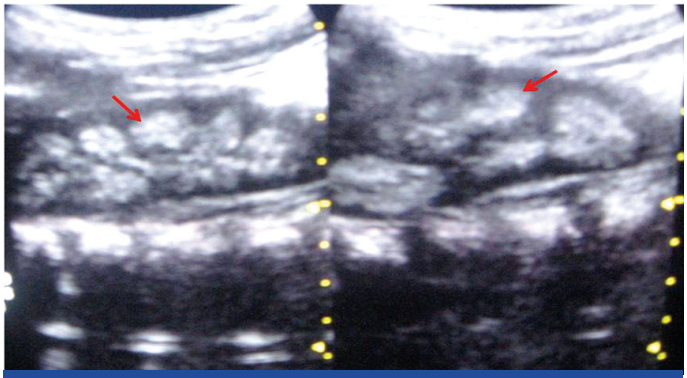
[Table/Fig-2]: Plain Radiograph shows notched, tongue like vertebral bodies, deformed ends of distal radius and ulna, and tapering of proximal aspects of metacarpals that characterize Mucopolysaccharidosis.



[Table/Fig-3]: Plain Radiographs of skull in a patient of Crouzon`s Syndrome showing craniostenoses.



[Table/Fig-4]: Plain Radiograph demonstrating characteristic shortening of first toe of both feet and abnormal soft tissue ossification in a case of Muchmeyer`s disease.



[Table/Fig-5]: Ultrasound image showing Nephrocalcinosis as hyper echoic areas in renal parenchyma in a case of renal tubular acidosis.

Nephrocalcinosis can also be demonstrated on a plain radiograph of the abdomen in patients in whom the end stage is reached in the form of renal osteodystrophy.

b. Similarly, patients of Lipoid Proteinosis exhibit characteristic intracranial calcifications on the plain radiographs.

c. Mucopolysacchridoses [Table/Fig-2] exhibit a proximal tapering of metacarpals, the deformed ends of the distal radius and the ulna, and the notching of vertebrae, that can be seen on plain radiographs as well.

d. Inborn errors of metabolism which resulted from adrenal hyperplasia showed an advanced bone age of around 9-11 years in a child who actually was 2 years of age.

e. Plain radiographs of the skull [Table/Fig-3] in a patient with Crouzon's syndrome showed the premature closure of the calvarial and the cranial base sutures, as well as those of the orbit and the maxillary complex (craniosynostosis). There was complete penetrance and a variable expressivity in this autosomal dominant disorder [6]. A mutation in the fibroblast growth factor receptor-2 (FGFR2) gene was the underlying cause, as the locus heterogeneity with causal mutations in FGFR2 caused Crouzon's syndrome and that in FGFR3 caused Crouzon`s syndrome with acanthosis nigricans [7].

f. Plain radiographs demonstrated the characteristic shortening of the first toe of both feet and abnormal soft tissue ossification in a case of Muchmeyer`s disease. It is an extremely rare, disabling disorder which causes the gradual ossification of the striated muscles, tendons, ligaments, fascia and aponeurosis [8]. Although it is usually

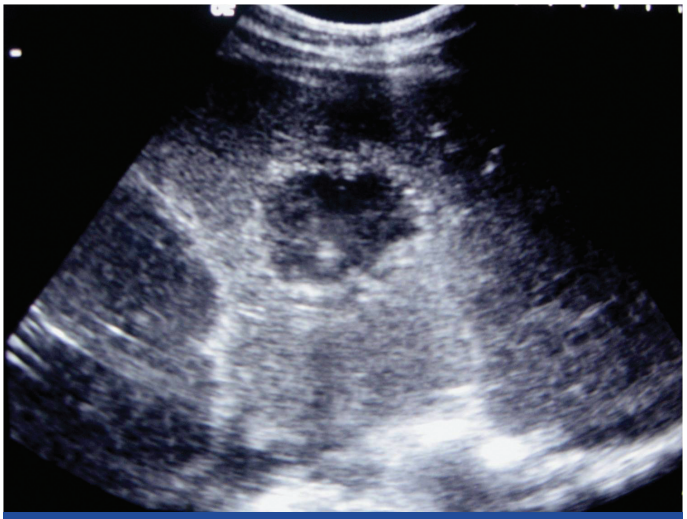
sporadic, it may be inherited as an autosomal dominant disorder that has a wide range of expressions [9].

2. **Ultrasound** non invasively demonstrates the details of the internal organs and the soft tissue structures without any exposure to the ionizing radiations as in the plain radiographs or Computed Tomography (CT).

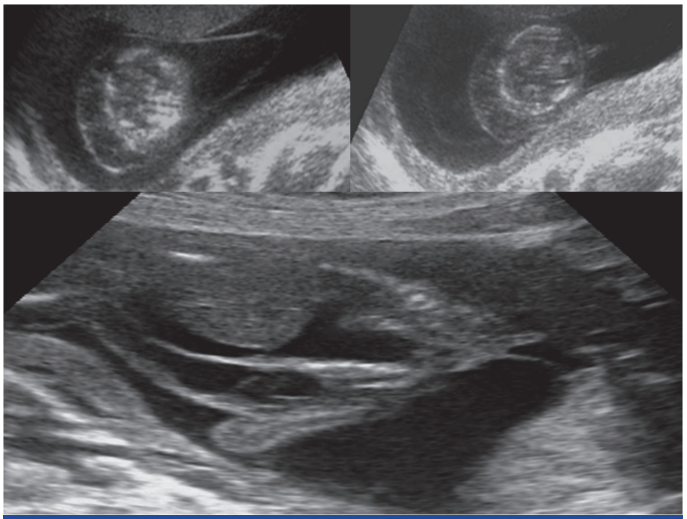
   a. Nephrocalcinosis [Table/Fig-5] in Renal Tubular Acidosis and renal osteodystrophy which was secondary to the malfunctioning of the Vitamin D metabolism could be demonstrated on the sonography of the kidneys which was carried out in a sick child who was made to undergo abdominal ultrasound as a routine procedure for non-specific pain.
   b. Similarly, ocular ultrasound can demonstrate ectopia lentis (the outward and upward subluxation/dislocation of the lens) in a patient of Marfans Syndrome.
   c. Hereditary tyrosinaemia is an autosomal recessive, enzymatic disorder that manifests as micro- and macro nodular cirrhosis in early childhood. Hepatocellular carcinoma occurs in approximately one-third of the affected children [10, 11].
   d. Unexplained male hydrops [Table/Fig-7] can be seen in Barth's Syndrome which is an X-linked multisystem disorder which is usually diagnosed in infancy and is characterized by cardiac problems like dilated cardiomyopathy, endocardial fibroelastosis, proximal myopathy, feeding problems, growth retardation, neutropaenia, organic aciduria and variable respiratory chain abnormalities [12].
   e. On ultrasound, retinoblastoma can be seen as a mass lesion which arises from the retina [Table/Fig-8]. A mutation in the long arm of chromosome 13 prevents the normal suppression of the development of retinoblastoma, resulting in retinoblastoma. MDM2 has been identified as the first modifier gene for retinoblastoma [13].

3. **CT scan** shows exquisite cross sectional details of the body structures. Although there is a risk of radiation exposure, the investigation is carried out only when the benefit outweighs the risks.

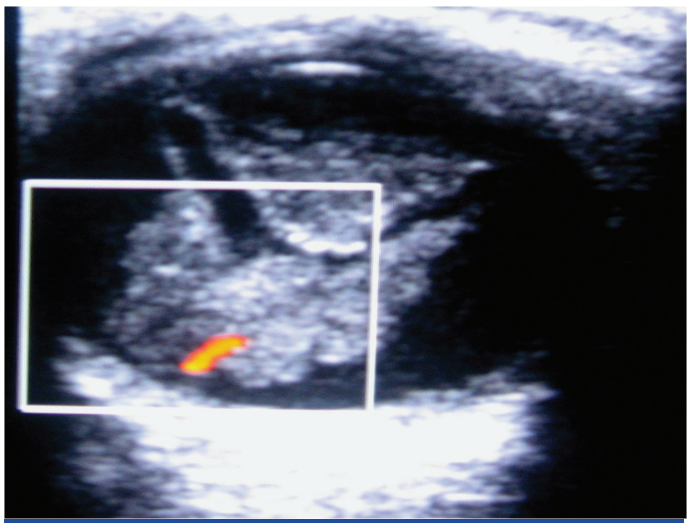
   a. Lipoid Proteinosis [Table/Fig-9] demonstrates bilateral symmetric comma shaped intracranial calcifications.
   b. Alexander's Disease shows bilateral frontal atrophy and symmetric hypo densities.
   c. Many IEMs have microcephaly. However, the clinical examination alone is insufficient in confirming whether it is pure microcephaly or it is just due to sutural fusion / craniostenoses. CT scan of the brain solves this dilemma by demonstrating unfused sutures in a patient who has a small appearing head size.
   d. Fibrous dysplasia (FD) is a congenital, non inheritable, genetic disorder in which the medullary bone is slowly replaced by fibro-osseous tissues, leading to the distortion and overgrowth of the affected bone, giving a characteristic ground glass appearance to the affected bone [Table/Fig-10]. It results from the mutation of gene



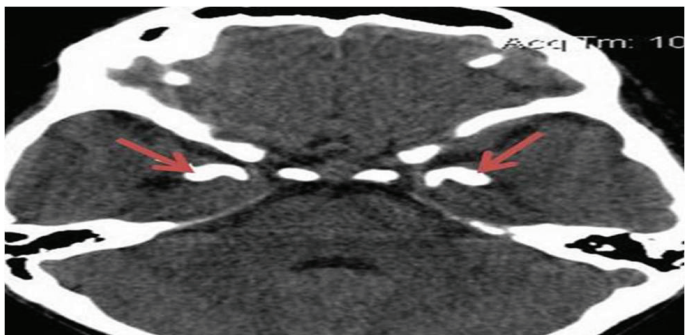
[Table/Fig-6]: Ultrasound showing hepatic nodule in hereditary tyrosinemia



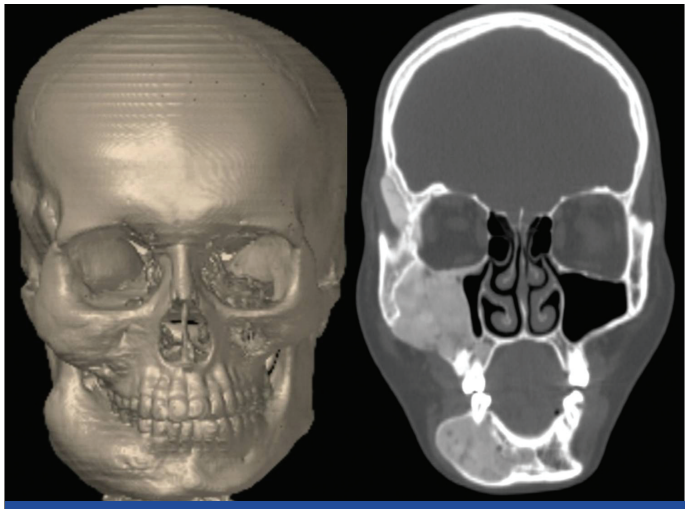
[Table/Fig-7]: Ultrasound showing fetal hydrops in Barth Syndrome



[Table/Fig-8]: Ultrasound showing Retinoblastoma



[Table/Fig-9]: Axial CT scan non contrast image shows bilaterally symmetric comma shaped hyperdense foci in medial temporal regions characteristically seen in patients of Lipoid Proteinosis.



[Table/Fig-10]: CT scan images showing expansile lesions with ground glass appearance in right sphenoid, maxilla and mandible in a case of Fibrous dysplasia.

which encodes for the alpha sub-unit of the stimulatory G protein in the bone marrow cells, leading to a locally increased stimulatory activity of adenyl cyclase and cAMP. This mutation causes an increased production of the C- fos protein and interleuekin-6, that results in a classic, dysplatic bone in FD [14].

4. **MRI** – shows the details of all the orthogonal planes without any risk of radiation exposure. It has the ability to strongly point towards an IEM as the cause of the patient's suffering, especially so, when other special biochemical investigations are not available / feasible / results are pending. Neuroimaging [15] can thus be an eye opener in the unexplained cases. IEM may be associated with structural malformations.

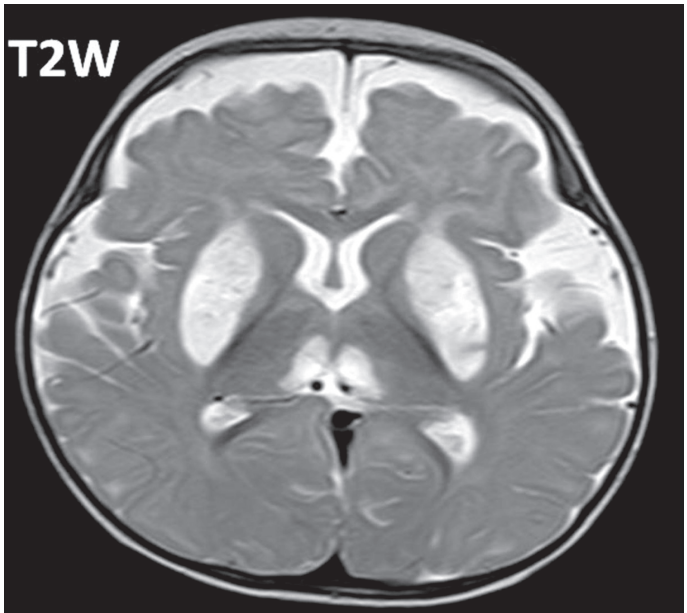
   a. Diffuse cortical migration and sulcation abnormalities are seen in Zellweger`s syndrome.
   b. Agenesis of the corpus callosum is seen in pyruvate decarboxylase deficiency, Menke's disease and non-ketotic hyperglycinaemia.
   c. Brainstem and cerebellar oedema are seen in Maple syrup urine disease.
   d. Subdural haematomas and frontotemporal atrophy suggest Glutaric aciduria.
   e. Hunter's disease is a rare, X-linked mucopolysaccharidosis and it shows [16] perivascular space enlargement, subarachnoid space enlargement, IIIrd ventricle dilatation, pituitary sella abnormalities, cranial hyperostosis, craniosynostosis, enlarged cisterna magna, dens hypoplasia, periodontoid thickening, spinal stenosis, platyspondylia and disc abnormalities, which are frequently detected.
   f. 3-Methylglutaconic aciduria type I is a rare inborn error of leucine catabolism. MRI revealed [17] an extensive white matter disease in a 10 year old boy. The follow-up MRI in the 10-year-old boy, who presented earlier with isolated febrile seizures, showed mild abnormalities in the deep white matter.

5. **Magnetic resonance spectroscopy (MRS):** The in vivo MR spectroscopy findings are typical for selected IEMs.

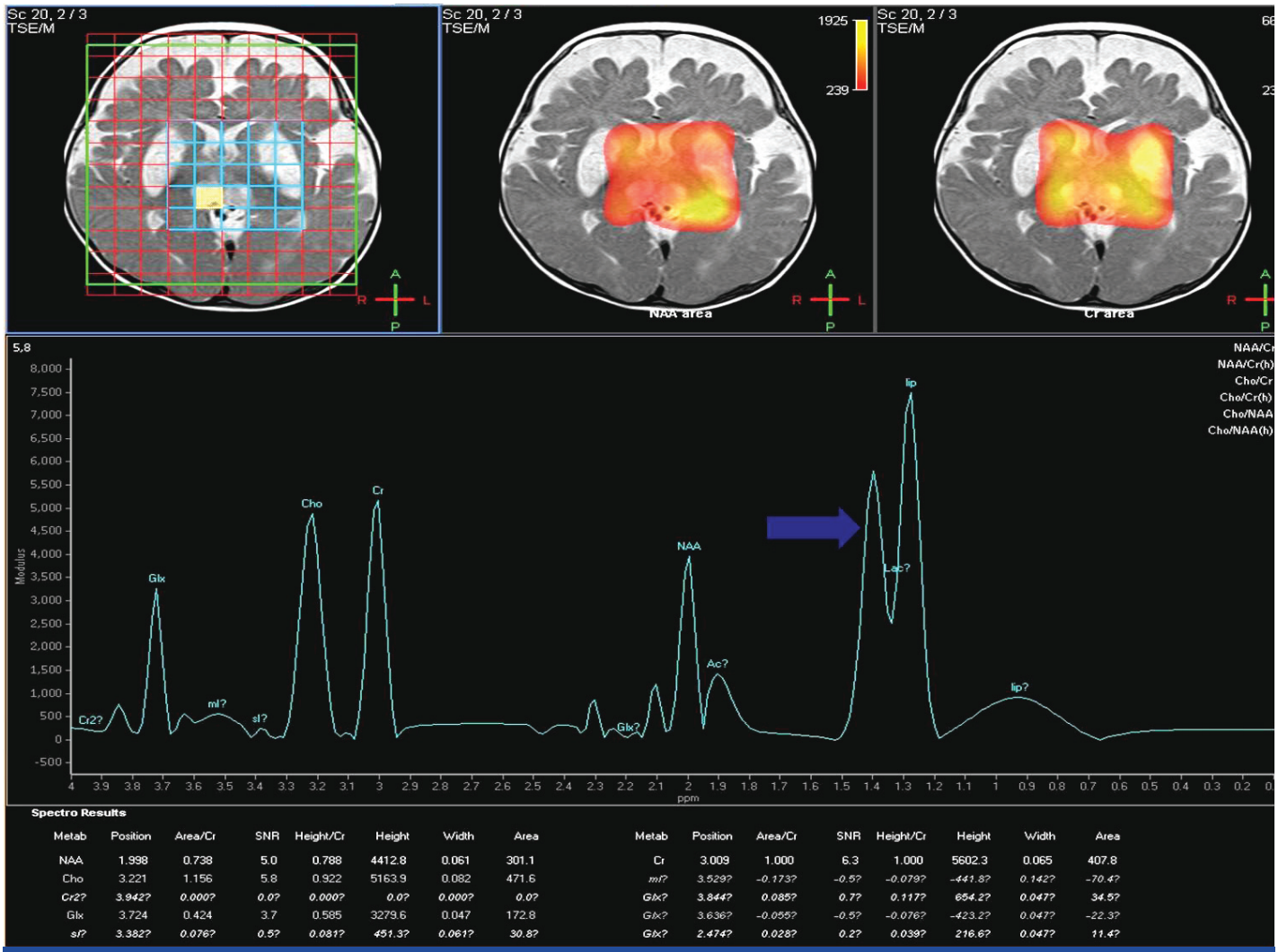
   a. The Adenylosuccinate lyase [18] (ADSL) deficiency is an inherited metabolic disorder which predominantly affects the central nervous system and manifests itself as seizures, muscular hypotonia, psychomotor delay and behavioural abnormalities. There is a characteristic accumulation of succinyladenosine (S-Ado) in the tissue and in the body fluids. The in vivo proton MRS measurements show a prominent signal at the 8.3 ppm in the gray and white matter brain regions of all the patients, that corresponds to the accumulated S-Ado.
   b. MR spectroscopy [19] in Pyruvate dehydrogenase (PDH) deficiency shows an elevated level of pyruvate at the 2.37 ppm. In addition, the findings of MRI of the brain [20,21,22] that raise a suspicion, include complete or partial agenesis of the corpus callosum, heterotopic gray matter, the absence of the medullary pyramids and the abnormal inferior olives, hydrocephalus and cerebellar dysplasia.
   c. The diagnosis of Leigh`s Disease can be strongly suggested by neuro imaging, [23,24,25] which shows bilateral, symmetric, focal hyperintensities in the basal ganglia, the thalamus, the substantia nigra, and the brainstem nuclei at various levels on the T2-weighted MRI images [Table/Fig-10] due to spongiform changes and vacuolation in the affected brain structures. The underlying defect can be at any of the sites in the enzyme pathway for the respiratory metabolism, leading to lactate accumulation in body, which is demonstrated in MRI Spectroscopy [Table/Fig-11]. The image of the brain can be seen as a lactate peak.

Although many conditions have a similar presentation, MRS offers valuable information for the individual patient for his/her diagnosis and therapy when it is integrated fully into the clinical setting [26].

The various characteristic radiological findings can thus aid in reaching a proper and prompt diagnosis of these errors of metabolism for an effective treatment and to obtain baseline studies to monitor the disease [27]. These findings that can cause terrors in the residents on the imaging studies of these patients, can in fact reduce the errors in diagnosing the inborn errors of metabolism and can at times be very conclusive when a paucity of the facilities and financial constraints prevent or delay the enzymology, histology and molecular studies.



[Table/Fig-11]: Axial MRI T2W image shows bilateral, symmetric focal hyperintensities in the basal ganglia and thalami that are unique to Leigh`s Disease.



Spectro Results

Metab	Position	Area/Cr	SNR	Height/Cr	Height	Width	Area
NAA	1.998	0.738	5.0	0.788	4412.8	0.061	301.1
Cho	3.221	1.156	5.8	0.922	5163.9	0.082	471.6
Cr2?	*3.942?*	*0.000?*	*0.0?*	*0.000?*	*0.0?*	*0.000?*	*0.0?*
Glx	3.724	0.424	3.7	0.585	3279.6	0.047	172.8
sI?	*3.382?*	*0.076?*	*0.5?*	*0.081?*	*451.3?*	*0.061?*	*30.8?*

Metab	Position	Area/Cr	SNR	Height/Cr	Height	Width	Area
Cr	3.009	1.000	6.3	1.000	5602.3	0.065	407.8
mI?	*3.529?*	*-0.173?*	*-0.5?*	*-0.079?*	*-441.8?*	*0.142?*	*-70.4?*
Glx?	*3.844?*	*0.085?*	*0.7?*	*0.117?*	*654.2?*	*0.047?*	*34.5?*
Glx?	*3.636?*	*-0.055?*	*-0.5?*	*-0.076?*	*-423.2?*	*0.047?*	*-22.3?*
Glx?	*2.474?*	*0.028?*	*0.2?*	*0.039?*	*216.6?*	*0.047?*	*11.4?*

[Table/Fig-12]: MRI Spectroscopy of brain shows elevated lactate peak marked by blue arrow which confirms the lactate accumulation in Leigh`s Disease

PREVENTIONAL ASPECTS

1) **Genetic counselling and prenatal diagnosis:** Most of the IEMs have a 25% recurrence risk, as they are inherited in an autosomal recessive manner. Therefore, when the diagnosis is known and confirmed in the index case, a prenatal diagnosis can be offered for the subsequent pregnancies [28]. On such occasions, a radiological modality like ultrasound is a very useful guide for obtaining the samples of the chorionic villus tissue or the amniotic fluid, as is required for the diagnosis.

2) **Neonatal screening:** It should be offered in affording families who are known to have such a disease or in whom one sibling has such a disease. The population screening [29,30] of the newborns as a form of preventive medicine, has attracted international interest due to the increased purchasing power of the middle classes in developing economies which are secondary to globalization, where it is strongly felt that that it is unfair to withhold the benefits of the first world medicine from infants in the under-privileged communities.

3) In sporadic cases where the diagnosis has not been made and where the patient expires before the complete evaluation, it becomes difficult to perform an autopsy, as the parents may not be willing to go for it. In such cases, whole body MRI is useful in the investigation of some inherited metabolic causes of sudden infant death, like in the diagnosis of type 2 carnitine palmitoyltransferase deficiency, which might prevent future deaths in the family. It is a good alternative when autopsy has been refused [31].

SUMMARY

To satisfactorily tackle IEM, an integrated approach is needed. The modes of presentation and the clinical features are not always characteristic and bear a resemblance to the routine day to day illnesses. Radiological investigations play an important role in being the first to raise a strong suspicion and in some instances, even to confirm a clinical suspicion of IEM. Early clinical and laboratory diagnosis along with adequate treatment can provide these children a meaningful normal life. Hence, the medical fraternity needs to be aware of the role of radio-diagnosis is evaluating IEM.

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