



Radio-imaging for detecting congenitally defective metabolic pathways: A review

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REVIEW

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Abstract

Congenitally defective metabolic pathways adversely affect the quality of life of patients as well as their care givers. Early diagnosis is therefore vital. Frequently, radio-imaging alone raises a strong suspicion and sometimes even provides conclusive evidence of defective metabolic pathways, when the patient presents with signs and symptoms that clinically fail to lead to a definitive diagnosis. This article discusses the role of radiological imaging that can lead to a strong suspicion, or even a diagnosis of these errors.

Key Words

Congenital metabolic defects, radiograph, ultrasound, CT scan, MRI, MR spectroscopy

Background

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 metabolic disorders.¹

These disorders are broadly classified¹ depending upon the metabolic pathways they affect the most: e.g. disorders of carbohydrate metabolism (glycogen storage disease),

amino acid metabolism (e.g. phenylketonuria), disorders of organic acid metabolism (e.g. alkaptonuria) etc.

More than 500 types of inborn error of metabolism have now been known to occur in humans.² Although isolated cases are rare, the combined data is staggering in terms of the effect on childhood health statistics. Hence early diagnosis is required to ensure a better quality of life.

In British Columbia¹, 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 targeting this specific question. However data^{3,4} suggests that out of 25 million annual births in India; 800,000 suffer from congenital malformation; 3.5 million have glucose 6 phosphate deficiency (G6PD); 25,000 have metabolic disorders; 20,000 have Down's Syndrome; 15,000 have congenital hypothyroidism; 14,000 have thalassaemias; and 5,000 have sickle cell anemias. When 4,400 patients suffering from mental retardation were biochemically screened, it was found that 256 cases (5.75%) were due to various inherited metabolic disorders.

Due to myriad forms of these diseases, affected patients present to clinics with countless manifestations.⁵ Signs and symptoms are usually very non-specific, such as nausea, vomiting, failure to thrive and so on. Sometimes seizures and abnormal movements may also be seen.

Hence frequently when unsuspected patients are referred for various radiological examinations, certain characteristic radiological findings may be the first to raise a strong suspicion of a metabolic abnormality and, at times, may provide conclusive evidence of this.

The role of radio-diagnosis

1. Plain Radiographs 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 might even change the overall diagnosis. Here are a few examples.

- a. Plain radiograph of knees asked for in a sick child with knee swelling (Figure 1) showed typical features of rickets and indicated improper Vitamin D metabolism, thereby aiding in diagnosing a metabolic defect in this unsuspected patient. Nephrocalcinosis can also be demonstrated on plain radiograph of the abdomen in patients in whom end stage is reached in the form of renal osteodystrophy.
- b. Similarly patients of Lipoid Proteinosis exhibit characteristic intracranial calcifications on plain radiographs.
- c. Mucopolysaccharidoses (Figure 2) exhibits proximal tapering of metacarpals, deformed ends of distal radius and ulna, and notching of vertebrae that can also be seen on plain radiographs.
- d. Defective metabolism resulting from adrenal hyperplasia shows advanced bone age of around 9–11 years in a child who actually is two years of age.



Figure 1: Photograph of swollen knees and plain radiograph of knees – AP view showing reduced bone density, demineralisation, metaphyseal changes typical of rickets



Figure 2: Plain radiograph shows notched, tongue-like vertebral bodies, deformed ends of distal radius and ulna, and tapering of proximal aspects of metacarpals that characterise Mucopolysaccharidoses

2. Ultrasound scans non-invasively demonstrate the details of internal organs and soft tissue structures without exposure to ionising radiations as in plain radiographs or Computed Tomography (CT).

- a. Nephrocalcinosis (Figure 3) in renal tubular acidosis and renal osteodystrophy secondary to malfunctioning of Vitamin D metabolism can be demonstrated on sonography of kidneys carried out in a sick child who is made to undergo abdominal ultrasound as a routine procedure or for non-specific pain.
- b. Similarly, ocular ultrasound can demonstrate ectopia lentis (outward and upward subluxation/dislocation of lens) in a patient with Marfan's Syndrome.

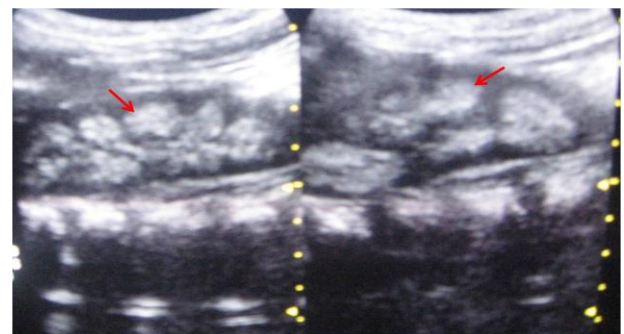


Figure 3: Ultrasound image showing nephrocalcinosis as hyperechoic areas in renal parenchyma in a case of renal tubular acidosis

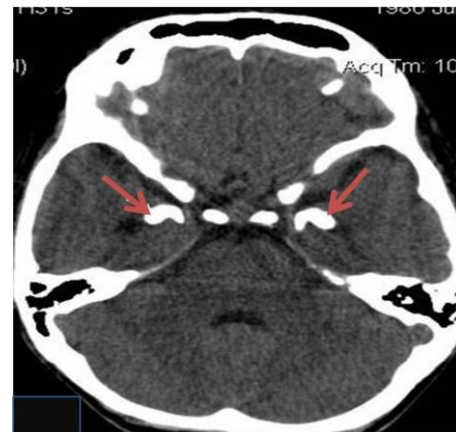


Figure 4: Axial CT scan image shows bilaterally symmetric comma shaped hyperdense foci in medial temporal regions characteristically seen in patients with lipoid proteinosis

3. CT scans show exquisite cross-sectional details of body structures. As there is associated risk from radiation exposure, this investigation is carried out only when the benefit outweighs the risks.



- a. Lipoid proteinosis (Figure 4) demonstrates bilateral symmetric comma shaped intracranial calcifications.
 - b. Alexander's Disease shows bilateral frontal atrophy and symmetric hypo-densities.
 - c. Microcephaly may be seen in patients with metabolic disorders. However clinical examination alone is insufficient in confirming whether it is pure microcephaly or just due to sutural fusion/craniostenoses. CT scan of brain solves this dilemma by showing unfused sutures in a patient who has a small appearing head size.
4. Magnetic Resonance Imaging (MRI) shows details in all orthogonal planes and without any risk of radiation exposure. It has the ability to strongly point towards metabolic defect as the cause of patients' suffering, especially when other special biochemical investigations are not available/feasible/results are pending. Neuroimaging⁶ can thus be an eye opener in unexplained cases. Associated structural malformations are also seen, such as:
- a. Diffuse cortical migration and sulcation abnormalities are seen in Zellweger's syndrome.
 - b. Agenesis of corpus callosum is seen in pyruvate decarboxylase deficiency, Menke's disease and non-ketotic hyperglycinemia.
 - c. Brainstem and cerebellar oedema are seen in Maple syrup urine disease.
 - d. Subdural hematomas and frontotemporal atrophy suggest Glutaric aciduria.

5. Magnetic resonance spectroscopy (MRS): In vivo MRS findings are typical for some conditions.

- a. Adenylosuccinate lyase⁷ (ADSL) deficiency is an inherited metabolic disorder predominantly affecting the central nervous system and manifesting as seizures, muscular hypotonia, psychomotor delay and behavioural abnormalities. There is characteristic accumulation of succinyladenosine (S-Ado) in tissue and body fluids. In vivo proton MRS measurements show a prominent signal at 8.3 ppm in grey and white matter brain regions of all patients, that corresponds to accumulated S-Ado.
- b. MR spectroscopy⁸ in pyruvate dehydrogenase (PDH) deficiency shows an elevated level of pyruvate at 2.37 ppm. In addition MRI brain⁹⁻¹¹ findings that raise suspicion include complete or partial agenesis of the corpus callosum, heterotopic grey matter, absence of the medullary pyramids and abnormal inferior olives, hydrocephalus and cerebellar dysplasia.
- c. The diagnosis of Leigh's disease can be strongly suggested by neuroimaging¹²⁻¹⁴ which shows bilateral, symmetric focal hyperintensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei at various levels on T2-weighted MRI due to spongiform changes and vacuolation in the affected brain structures. MRI brain images (Figure 5) show bilateral symmetrical abnormal signal intensities involving basal ganglia, thalami, cerebral peduncles, dorsal medulla and peri-aqueductal grey matter. They appear hypo-intense on T1W images and are hyper-intense on T2W and FLAIR images. No significant enhancement was seen in post-contrast study (TIW-PC). The underlying defect can be at any of the sites in the enzyme pathway for respiratory metabolism leading to lactate accumulation in body that is demonstrated in MRI spectroscopy (Figure 6) image of brain as lactate peak.

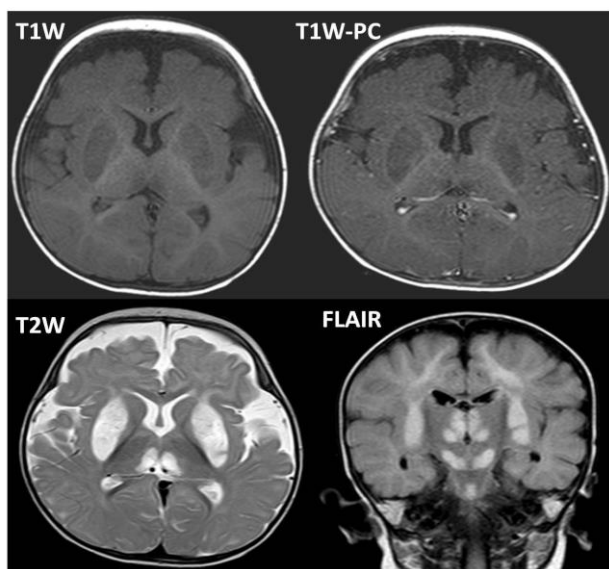


Figure 5: MRI brain images show bilateral symmetrical abnormal non enhancing signal intensities.

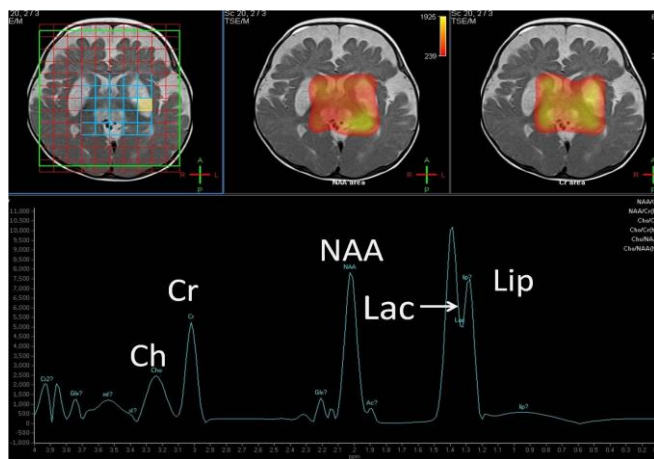


Figure 6: MRI spectroscopy of brain shows elevated lactate peak marked by blue arrow which confirms the lactate accumulation in Leigh's disease

Although many conditions have a similar presentation, spectroscopy offers valuable information for the individual patient in diagnosis and therapy when integrated fully into the clinical setting.¹⁵

With economic prosperity many higher radiological imaging modalities such as MRI are now routinely available. Characteristic imaging findings on MRI coupled with assessment of the metabolic abnormalities provided by MRI spectroscopy helps in early suspicion and sometimes confirmation of such entities. This can be life-saving especially when final diagnosis that is required from studies on enzymes, histological methods or molecular and genetic analysis takes longer duration. In fact demonstration of these abnormal metabolites by MRI spectroscopy has helped to identify the deficient enzyme in two new groups of diseases, creatine deficiencies and polyol anomalies.¹⁶ Positron emission tomography (PET) after injection of [18F] Fluoro-L-DOPA has been validated as a reliable test to differentiate diffuse and focal congenital hyperinsulinism and is now a major differential diagnosis tool in infantile hyperinsulinemic hypoglycaemia.¹⁶ Thus radiological innovations are adding newer perspectives to neuroimaging.^{17, 18}

Prevention aspects

1. Genetic counselling and prenatal diagnosis: Most metabolic conditions 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, prenatal diagnosis can be offered, for any subsequent pregnancies.¹⁹ On such occasions, a radiological investigation such as ultrasound is a very useful guide for obtaining samples of chorionic villus tissue or amniotic fluid required for diagnosis.

2. Neonatal screening: should be offered in affording families who are known to have such a disease or in whom one sibling has such disease. Population screening^{20,21} of newborns as a form of preventive medicine has attracted international interest due to the increased purchasing power of middle classes in developing economies secondary to globalisation where it is strongly felt that that it is unfair to withhold the benefits of first world medicine from infants in under-privileged communities.

Conclusion

To satisfactorily tackle congenital metabolic defects, an integrated approach is needed. Modes of presentation and clinical features are not always characteristic and have resemblance to 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 confirm a clinical suspicion. Early clinical and laboratory diagnosis along with adequate treatment can provide these children with a meaningful normal life. Hence the medical fraternity needs to be aware of radio-imaging for congenitally defective metabolic pathways.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests

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PEER REVIEW

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