MRI IN PAEDIATRIC INHERITED METABOLIC BRAIN DISORDERS

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ABSTRACT

AIMS AND OBJECTIVES

To emphasize the role of MRI in paediatric inherited metabolic brain disorders and to study the varied spectrum of imaging findings in these disease entities and to highlight the importance of image based classification.

MATERIALS AND METHODS

In this study, we reviewed MRI of the brain of 26 paediatric patients (17 male, 9 female; mean age: 7 years, range: 1 month – 15 years) with neurological complaints and had clinical suspicion of inherited metabolic brain disorder on MRI. MRI sequences reviewed included axial T1-, T2-weighted, FLAIR, diffusion weighted and sagittal and coronal T2 weighted images. Post-gadolinium T1-weighted and MR Spectroscopy images were also reviewed when available. MRI findings were interpreted in conjunction with clinical and laboratory findings wherever necessary. The varied spectrum of imaging appearances of paediatric inherited metabolic brain disorders noted by methodological and practical image based approach.

RESULTS

The distribution of the various inherited metabolic disorders was as follows: 13 cases of Leigh's disease, 4 cases of Metachromatic Leukodystrophy, 2 cases of Pantothenate Kinase Deficiency, 2 cases of Gangliosidosis, 2 cases of Wilson's disease, one case of Alexander's disease, one case of Canavan's disease, one case of Glutaric aciduria diagnosed from the image based pattern in conjunction with the clinical data. Based on the pattern of brain involvement on MRI, these disorders were classified into three categories: disorders with predominant white matter involvement, disorders with predominant gray matter involvement and disorders with involvement of both gray and white matter. There were characteristic metabolic peaks on MRS in cases of Leigh's disease and Canavan's disease.

CONCLUSION

An image based approach to paediatric inherited metabolic brain disorders helps in diagnosis of varied presentation and knowledge of this practical approach is very useful to the radiologist.

KEYWORDS

Image Based Classification, Pattern Recognition, Periventricular White Matter, Subcortical 'U' Fibres

HOW TO CITE THIS ARTICLE: Tirumani SB, Prasad RY, Mudunoor VK, et al. MRI in paediatric inherited metabolic brain disorders. J. Evolution Med. Dent. Sci. 2016;5(69):4967-4971, DOI: 10.14260/jemds/2016/1128

INTRODUCTION

Inherited metabolic disorders encompass a wide spectrum of neurodegenerative disorders affecting myelination.[1] Each disorder has distinctive clinical, biochemical, pathologic and radiological features.[2] The diagnosis of these needs a clinico-radiological approach as symptoms vary both between disorders and in the degree of severity in patients with the same disorder.[3] MRI has virtually replaced all other imaging modalities including CT in the evaluation of inherited metabolic brain disorders due to its excellent Gray-White matter resolution and multiplanar imaging capability.[4]

In this article, we report our experience with MR in 26 patients with inherited metabolic brain disorders and discuss the importance of image-based classification of these diseases.

Financial or Other, Competing Interest: None.
Submission 05-02-2016, Peer Review 01-06-2016,
Acceptance 06-06-2016, Published 26-08-2016.
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DOI: 10.14260/jemds/2016/1128

MR scans are routinely obtained in infants and children with delayed neurologic development and clinical suspicion of inherited metabolic brain disorder. We then delineate and subsequently use an approach pioneered by A. James Barkovich that is primarily based on anatomic location and specific imaging features.

MATERIALS AND METHODS

In this Institutional Review Board approved retrospective study and with waiver informed consent, twenty six clinically suspected patients with inherited metabolic brain disorder during a period of one year (December 2014 to January 2016) referred to Osmania General Hospital formed the basis of the present study. All the patients with acquired causes of neurological dysfunction were excluded from the study group. MRI was performed on a 1.5 Tesla electromagnet (General Electrical Medical Systems). The study included T1, T2 and FLAIR, DWI axials and T2 sagittal and coronal images. We also included contrast enhanced MRI and MR Spectroscopy whenever necessary. The findings were observed and interpreted in conjunction with clinical findings and also lab findings wherever necessary. The varied spectrum of imaging appearances of paediatric inherited

metabolic brain disorders noted by methodological and practical image based approach.

OBSERVATION AND RESULTS

Leigh's disease	13
MLD	4
Wilson's disease	2
Gangliosidosis	2
PKAN (NBIA Type 1)	2
Canavan's disease	1
Alexander's disease	1
Glutaric aciduria	1

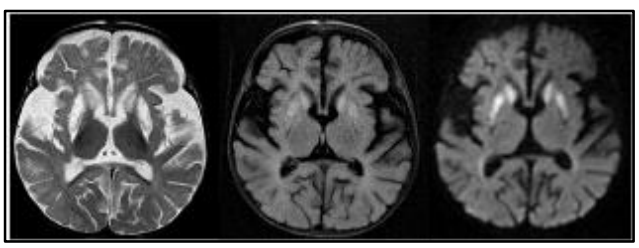


Fig. 1: Leigh's Disease

The criterion of image interpretation was the image based classification, which grossly divides these disorders on the pattern of involvement of gray and white matter. It is categorised as predominant white matter involvement with a sub-category of predominant periventricular involvement which includes the four cases of Metachromatic Leukodystrophy. The other group with predominant deep gray matter involvement are two cases of Wilson's disease and two cases of Pantothenate Kinase deficiency. The rest of cases belonged to the third category with involvement of both gray and white matter as in one case of Canavan's and one case of Alexander's disease, two cases of Gangliosidoses, one case of Glutaric aciduria and thirteen cases of Leigh's disease.

Out of the 26 cases, we had 13 cases of Leigh's disease and MR revealed bilateral basal ganglia hyperintensities on T2 predominantly involving putamen and caudate. MRS showed lactate peak in 10 cases.

In one case the findings were atypical with bilateral symmetrical T2WI, FLAIR hyperintensities with restricted diffusion noted in the periphery of mid-brain and periaqueductal gray matter and also in the ventral aspect of medulla.

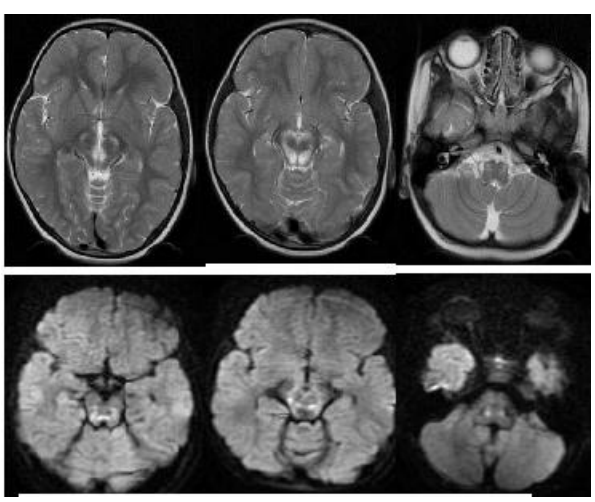


Fig. 2: Leigh's Disease with Mid Brain and Pons Involvement

Four cases were Metachromatic Leukodystrophy with imaging findings of symmetric periventricular white matter T2/FLAIR hyperintensities with one case

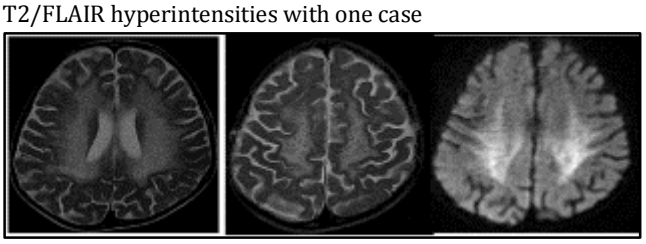


Fig. 3: Metachromatic Leukodystrophy

showing the typical Tigroid pattern due to sparing of perivascular white matter. One case showed Cerebellar hyperintensities.

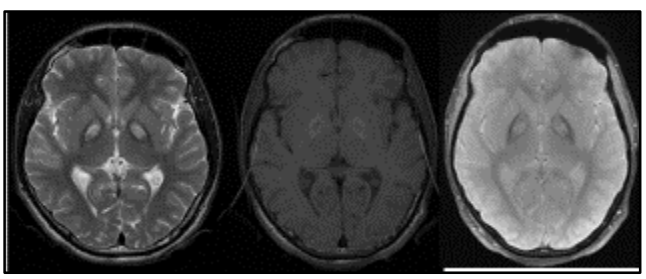


Fig. 4: PKAN (NBIA Type 1)

Two cases of Pantothenate Kinase deficiency (Hallervorden-Spatz disease) were noted showing T2WI/FLAIR hyperintensity with surrounding hypointensity in bilateral globus pallidus noted.

Alexander's disease with Megalencephaly and Periventricular T2 white matter hyperintensities in the bilateral frontal region was seen in one case. On contrast, the lesion showed no contrast enhancement. On MRS, decreased NAA peak was noted.

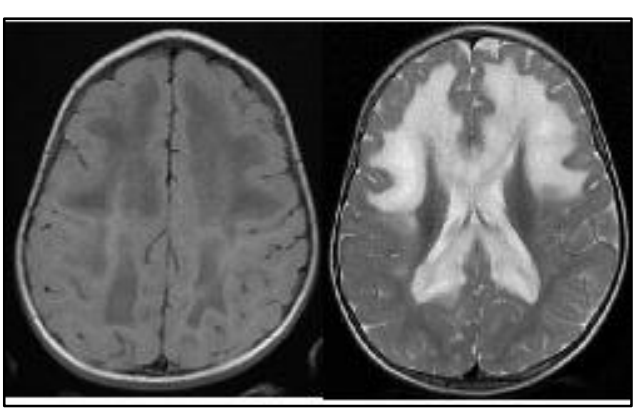


Fig. 5: Alexander's Disease

One case of Canavan's with megalencephaly, diffuse subcortical and periventricular white matter T2 hyperintensity in the bilateral fronto-parieto-occipital regions and also in the cerebellum. On MRS, characteristic NAA peak is noted.

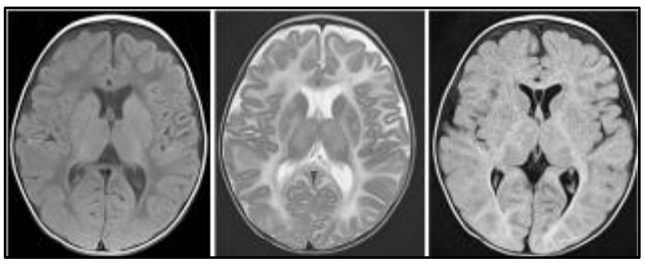


Fig. 6: Canavan's Disease

Gangliosidosis with generalised T2/FLAIR hyperintensity involving subcortical as well as deep white matter in bilateral cerebral hemispheres and cerebellum was seen in two cases. Bilateral caudate head and Thalami are bulky with T2 hypointensity. One patient had cherry red spot in the eye.

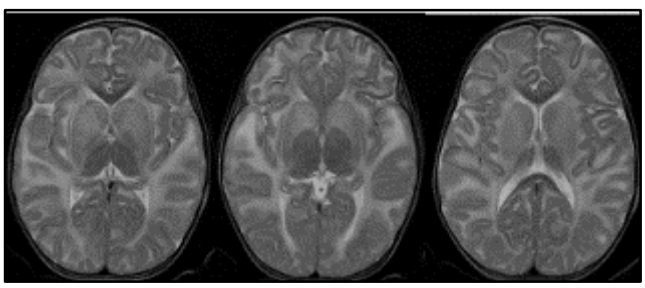


Fig. 7: Gangliosidoses

One case of Glutaric aciduria with prominent sulcal spaces noted in bilateral fronto-parieto-temporal lobes with open sylvian fissures and sub-acute sub-dural haemorrhage, T2WI/FLAIR hyperintensities showing subtle restriction on DWI noted in bilateral basal ganglia.

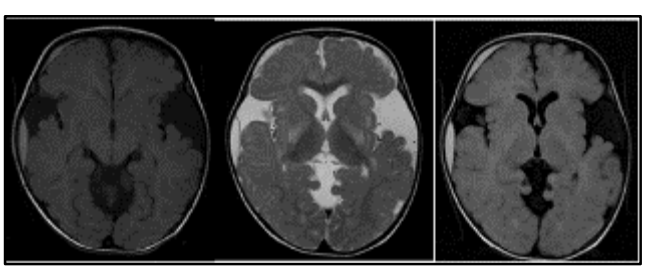


Fig. 8: Glutaric Aciduria

The three "signature" imaging findings of classic Glutaric Aciduria are: (1) Macrocrania, (2) Bilateral widened ("open") sylvian fissures, and (3) Bilaterally symmetric basal ganglia lesions.

Two cases of Wilson's disease, both patients had KF ring. One case had bilateral basal ganglia involvement and the other had bilateral symmetric T2WI and FLAIR hyperintensities in bilateral caudate nuclei, lentiform nuclei, ventrolateral thalami, mid brain, periaqueductal gray matter and the pons. The lesion in the bilateral thalamus, lentiform nuclei, mid-brain and pons are restricted on DWI. Linear FLAIR hypointensity noted in the bilateral lentiform nuclei suggesting cystic changes.

DISCUSSION

Inherited metabolic disorders is a wide-spectrum of disease entities with an enigmatic overlap of neurological and imaging findings. MRI has given a new perspective to approach these metabolic disorders due to its excellent spatial resolution and various sequences.[5] MRI can help narrow the differential diagnosis

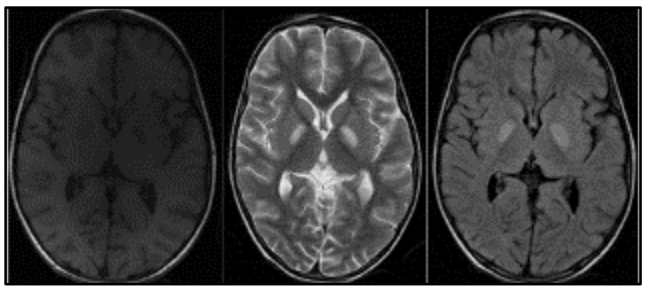


Fig. 9: Wilson's Disease

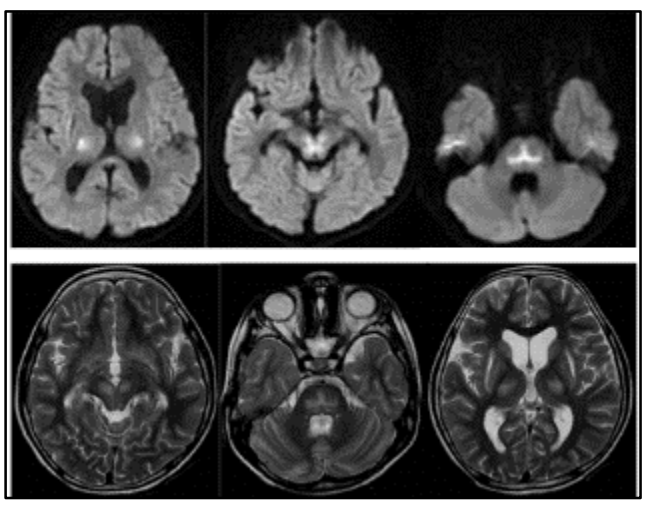
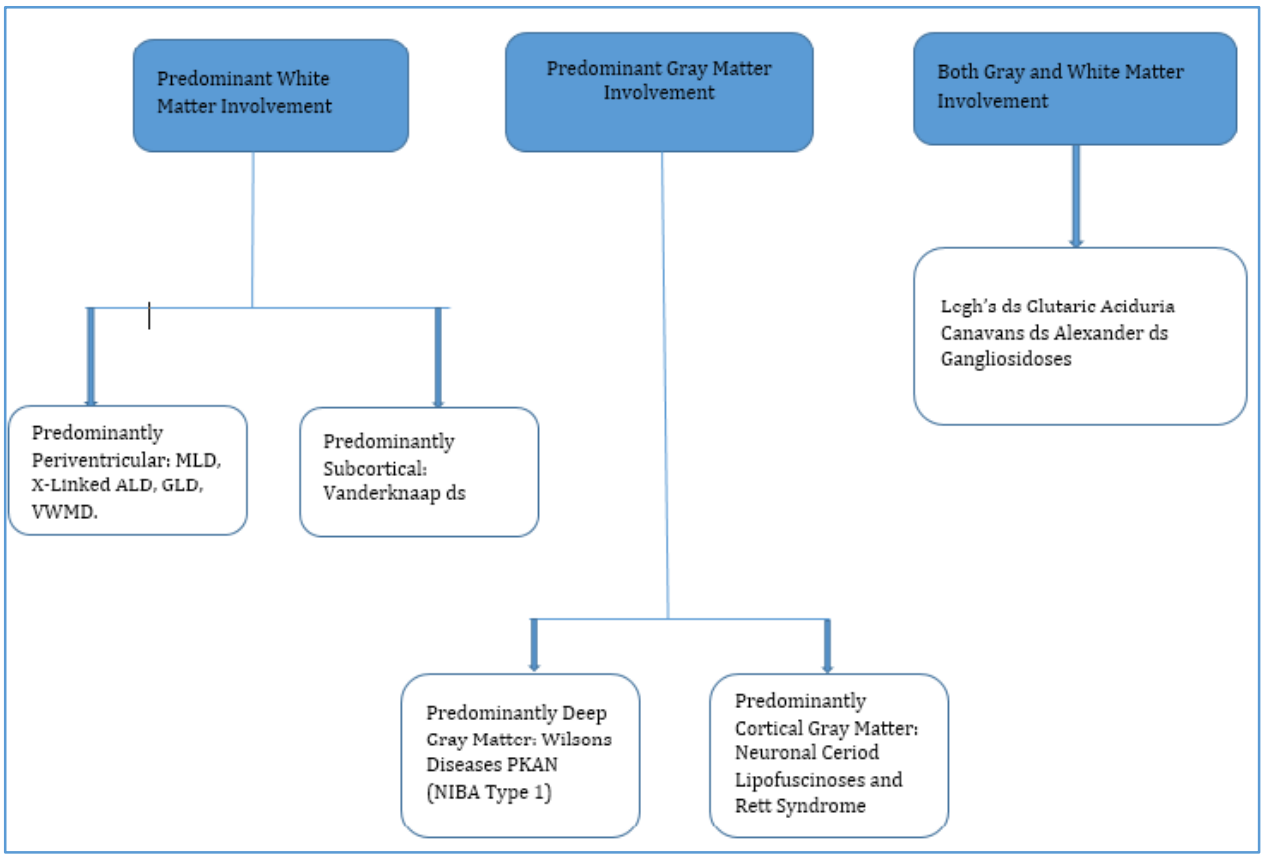


Fig. 10: Wilson's Disease

of these inherited paediatric metabolic disorders and this in conjunction with clinical and lab evaluation can help categorise the type of disorder.

Many classification systems have been used for categorising these diseases like organelle based approach, based on specific metabolic pathway and also based on anatomical location and specific imaging features.[6] The third approach of image based classification being pioneered by A. James Barcovich is best as a Radiologist can practically better approach the disease entity based on imaging findings.[7] It is important to submit the patient to a brain MRI early in the course of the disease, when some key features are more evident (Barkovich, 2007).[8] MRI occasionally points to a diagnosis and allows the reduction of the biochemical and genetic work-ups.



Imaging based approach categorises the inherited metabolic brain disorders as those involving predominantly white matter, predominantly gray matter and those involving both gray and white matter.[9] Amongst those involving predominantly white matter can be further categorised as predominant involvement of periventricular white matter as in Metachromatic leukodystrophy, Classic X-linked adrenoleukodystrophy, Globoid cell leukodystrophy (Krabbe disease), vanishing white matter disease and those with predominant subcortical white matter involvement as Van Der Knaap disease.

Metachromatic leukodystrophy has predominant periventricular white matter involvement with tigroid pattern and spares the subcortical U fibres until late in the disease.[10] It may have butterfly pattern of involvement. It also may have corpus callosal involvement, but late cerebellar involvement and shows no enhancement on contrast administration.

The other entity with predominant periventricular pattern of involvement is X-linked adrenoleukodystrophy, but the condition has posterior periventricular involvement and shows enhancing active demyelinating zone on contrast.[11] It can also have splenium involvement.

Krabbe's or globoid cell leukodystrophy also has predominant periventricular white matter involvement, but also has hypointense thalami due to calcifications[12] and early cerebellar involvement seen as alternating halos.[13]

Vanishing white matter disease also has periventricular involvement early in disease and later may cavitate. But corpus callosum, internal capsule and basal ganglia are spared.[14]

Van der Knaap's disease or Megaloencephalic leukodystrophy with subcortical cysts has megalencephaly with early involvement of subcortical U fibres and with cyst formation. The basal ganglia are spared; the corpus callosum and internal capsule are usually normal.

Another category of white matter involvement is hypomyelination disorders like Pelizaeus-Merzbacher disease. The typical imaging appearance of PMD is nearly complete lack of myelination with tigroid appearance due to sparing of perivascular white matter.

The second category of disorders includes those involving predominantly gray matter. This group is further divided into as those affecting the deep gray matter as in brain metabolite accumulation disorders like Wilson's disease with copper accumulation and PKD or NBIA type 1 with Iron deposition. The cortex is involved in rare disorders like neuronal ceroid lipofuscinoses and Rett syndrome.

Globus pallidus hypointensity with or without central hyperintensity is highly characteristic of PKAN[15] (Pantothenate Kinase-Associated Neuropathy) or Hallervorden-Spatz disease. All patients with PANK2 mutations had the specific pattern of T2-WI globus pallidus central hyperintensity (Destruction and gliosis) with surrounding hypointensity (Iron deposition) known as the eye-of-the-tiger sign.[16]

The most common neuro-radiological finding of Wilson's disease on MR is bilaterally symmetric T2/FLAIR hyperintensity in the putamina (70%), caudate nuclei (60%), ventrolateral thalami (55-60%), and midbrain (50%) (31-41). Hyperintensity can sometimes be seen in the pons (20%), medulla (10-15%) and cerebellum (10%). The cerebral (25%) and cerebellar WM (10%) can show focal or diffuse confluent hyperintensities. The giant panda appearance is seen in only 10% of cases.

Third group of disorders involve both gray and white matter includes Mucopolysaccharidoses, Gangliosidoses, Canavan's disease, Alexander disease and Mitochondrial disorders like Leigh's disease and Glutaric aciduria. In Mucopolysaccharidoses, T2 scans show CSF-like hyperintensity in the enlarged PVSs. The surrounding WM may show patchy or confluent hyperintensity.

In gangliosidosis, the globi pallidi and ventral thalami often appear profoundly shrunken and hypointense on T2WI. The WM appears variably T2/FLAIR hyperintense.

Canavan's disease has megalencephaly and MRI shows symmetric areas of diffuse confluent white matter areas of T1 and T2 prolongation.[17] The subcortical U fibers preferentially affected in the beginning of the disease. Globi pallidi are frequently involved as well as thalami. In some cases internal and external capsules (Cheon et al, 2002), cerebellar white matter and brain stem can also be affected (Matalon and Bhatia, 2009). In the later stages, there is a diffuse atrophy of white matter.

Alexander disease shows megalencephaly[18] and T1 hypointensity and T2/FLAIR hyperintensity in the frontal WM, caudate nuclei and anterior putamina.

In glutaric aciduria, MRI reveals symmetric widening of the Sylvian fissure, frontotemporal volume loss and delayed myelination. Putamen T2 hyperintensity is predominantly seen either alone or in combination with the caudate nucleus. Globus pallidus is less affected. Later in the course of disease, periventricular white matter T2 hyperintensity, basal ganglia and cerebral atrophy are seen. Sometimes imagiological studies reveal acute or chronic subdural haematomas.

Imaging findings in Leigh syndrome[19] are symmetrical T1 and T2 prolongation on MRI in the basal ganglia and thalami. Lesions can involve the substantia nigra, periaqueductal gray matter within the midbrain, inferior colliculus, inferior olivary nuclei, inferior cerebellar peduncles, medulla, solitary tract in the medulla, central tegmental tract and reticular formation in the dorsal pons. Less often, the red nuclei and cerebellar dentate nuclei are involved. Basal ganglia are often affected before the brainstem, but in some patients brainstem lesions appear without basal ganglia alterations. DWI shows reduced diffusion in acute lesions and increased diffusion in chronic ones. MRS reveals increase in lactate and a small decrease of NAA in lesions and supports the diagnosis of Leigh's disease.

Relevant use of these neuroimaging tools can be very beneficial for categorising these disorders into more manageable groups, and occasionally allows a specific diagnosis to be made. MRI shows high sensitivity and accuracy in the detection of some of these disorders and assessment of their severity. MRS[20] can be useful adjunct in making the diagnosis of inherited paediatric metabolic brain disorders when accompanied with specific pattern recognition.

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