



Brain Magnetic Resonance Imaging in Organic Acidemias: A Single Center Experience

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Abstract:

Background: Organic acidemias (OAs) are a group of inherited diseases with a defect of amino acid metabolism, unless treatment is initiated early in life, they cause serious central nervous system (CNS) complications as seizures, encephalopathy and others. Pre-symptomatic diagnosis is achieved within neonatal screening programs, otherwise the diagnosis is delayed and challenging.

Aim of work: To search for a specific magnetic resonance imaging (MRI) diagnostic finding common to OAs.

Material and Methods: This cross-sectional descriptive study included 42 children with confirmed organic acidemias following up at the Neurometabolic Clinic at Center for Social and Preventive Medicine, Pediatric Hospitals, Cairo University, Egypt. MRI brain scans were performed on a (1.5 T Aera machine).

Results: The study included 42 children with a median age of 36 months. Of them 29 (69%) were males and 13 (31%) were females, with male to female ratio of 2.23:1. Glutaric academia type 1 was confirmed in 26 (61.9%) followed by methylmalonic academia in 7 (16.67%), isovaleric academia in 3 (7.14%), propionic academia in 3 (7.14%), pyroglutamic academia in 2 (4.76%) and D2 hydroxy glutaric academia in 1 (2.38%). Abnormal signal in basal ganglion was encountered in 20 (47.6%), followed by cortical atrophy in 11 (26.2%), white matter changes in 11 (26.2%), temporal lobe hypovolemia in 10 (23.8%), ventricular dilatation in 6 (16.7%), arachnoid cyst in 4 (9.5%), normal MRI brain in 3 (7.1%) and encephalomalacia in 2 (4.8%). No specific imaging finding was associated with OAs or its type.

Conclusion: MRI findings of brain are common but not unique in organic acidemias or its types, but is not sensitive or specific. Normal MRI brain does not exclude the diagnosis of OAs.

Level of Evidence of Study: IV (1).

Keywords: Organic acidemias; magnetic resonance imaging; MRI; metabolic disorders.

Abbreviations: ADC: Apparent diffusion coefficient; Ax: Axial; C2: acetylcarnitine; C3: propionylcarnitine; (C5-DC): glutarylcarnitine; CNS: Central nervous system; DWI: Diffusion-weighted imaging; FLAIR: fluid attenuation and inversion recovery; FTT: Failure to thrive; GA-1: glutaric academia type 1; GDD: global developmental delay; IV: Isovaleric acidemia; MMA: methylmalonic acidemia; MRI: Magnetic resonance imaging; NBS: newborn screening; OAs: Organic acidemias; PA: propionic acidemia; T1W: T1-weighted; T2W: T2-weighted; TMS: tandem mass spectroscopy.

Introduction

Organic acidemias (OAs) are a group of metabolic disorders caused by enzymatic deficiencies in the catabolic pathway of branched-chain amino acids, leading to the accumulation of organic acids in body fluids and tissues (2). More than 65 specific organic acids that can affect these pathways have been identified (3). Many enzymes in the converging catabolic pathways are responsible for the characteristic clinical presentations of OAs and other in born errors of metabolism (4). A wide spectrum of clinical pictures ranges from asymptomatic as identified by the newborn screening (NBS), to early in life during the neonatal period as acute metabolic



collapse, or in childhood as unexplained global developmental delay (5, 6). The common symptoms of OAs are poor feeding, vomiting, lethargy, failure to thrive, developmental delay, liver affection, osteoporosis, hypotonia, seizures, ataxia, and disturbed conscious level (7). Early diagnosis and the pre-symptomatic initiation of appropriate therapy are crucial to improving the general condition of the patient, decreasing long-term neurological outcomes, and preventing death (7). Brain damage is also related to the sustained acidosis, it causes brain edema, brain injury, and morphological damage irrespective of the etiology of the acidosis. The effects may be immediate and/or delayed and long standing (8). The effects of acidosis are evident as bilateral basal ganglia T2/ fluid attenuation and inversion recovery (FLAIR) hyperintensity or specifically as lentiform fork sign on magnetic resonance imaging (MRI) (9).

MRI is the most sensitive and specific noninvasive neuroimaging that helps in the limiting the differential diagnosis of inborn errors of metabolism (10). MRI shows nearly all aspects of the brain: structural, physiological, metabolic, and functional (11). Radiological findings of MRI were reported to differ according to the different types of OAs (12). Propionic acidemia and methylmalonic acidemia show a picture of acute brain swelling with diffuse signal intensity abnormalities and hyperintense signals in the globus pallidus bilaterally at T2-weighted MRI in isovaleric acidemia (8). Enlargement of subarachnoid CSF spaces and widening of the Sylvian fissures were reported to be characteristic of glutaric aciduria type 1 (13).

We aimed to search for a specific magnetic resonance imaging (MRI) diagnostic finding common to OAs.

Subjects and Methods

This cross-sectional descriptive study included 42 children with confirmed OA diagnosis. They followed up at the Neurometabolic Clinic at the Center for Social and Preventive Medicine, Pediatric Hospitals, Cairo University, Egypt. The study was approved by the Research Ethics Committee, Faculty of Medicine, Cairo University, Egypt (IRB: MS-51-2020). Care takers consented to the trial. Data were collected from files; any data that allows patients identification was omitted, and patients were numerically coded during the data collection phase, and these codes were used in all subsequent research phases.

Participants

This study included 42 children with confirmed OA among 6890 children who attended the Neurometabolic Clinic during 2018 and 2021. Diagnosis of OA was suggested by clinical symptoms like unexplained neurological or digestive symptoms and/or a positive family history of OA cases or unexplained deaths, low serum glucose, abnormal electrolytes, serum ketone bodies, arterial blood gases, ammonia, and lactate levels. Confirmation of diagnosis relied upon biochemical metabolic workup relied tandem mass spectrometry (TMS) analysis of the acylcarnitine profile in dried blood spots and quantitative gas chromatography-mass spectrometry (GC-MS) analysis of the organic acids in urine. The confirmation was according to criteria in table 1.

Methods

MRI brain scans were performed on a 1.5 T Aera machine, (Siemens Magnetom, Germany) The imaging included T1-weighted (T1W), axial (Ax), sagittal, fast spin echo, T2-weighted (T2W), FLAIR, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC). Oral sedation (10% chloral hydrate, 1 mg/kg/dose) was given 15 minutes before the MRIs to the children who needed to be sedated.

Statistical Analysis

The collected data were computerized and statistically analyzed using Statistical Package for Social Sciences (SPSS 24 Inc. Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as median and range.

**Table 1.** Confirmatory tests relied upon for diagnosis of organic acidemia in the current study

	TMS	Increased urine organic acids
GA-1	Low free carnitine, high C5-DC- carnitine	Glutaric, 3-hydroxyglutaric, glutaconic acid
MMA	High C3, high C3-C3/C2 ratio	Methylmalonic, methylcitric, hydroxy propionic, 3-hydroxyisovaleric, propionylglycine
IVA	No abnormality	Isovalerylglycine, 4-hydroxyvaleric, 3-hydroxyisovaleric acids
PA	High C3	Methylcitric, 3-hydroxypropionic, 3-hydroxyisovaleric, 3-hydroxybutyric, 2-methyl-3-hydroxybutyric, propionylglycine
Pyroglutamic acidemia	No abnormality	Elevated pyroglutamate (5-oxoproline)
D2 hydroxy glutaric acidemia	No abnormality	Elevated D-2-hydroxyglutaric acid (D-2-HG)

C2: acetylcarnitine; C3: propionyl carnitine; (C5-DC): glutarylcarnitine; GA-1: glutaric acidemia type 1; IV: isovaleric acidemia; MMA: methylmalonic acidemia; PA: propionic acidemia; TMS: tandem mass spectroscopy.

Results

The study included 42 children with a median age of 36 months (range = 1 and 144 months) (mean \pm SD= 55.2 \pm 43 months). Of them 29 (69%) were males and 13 (31%) females, with a male-to-female ratio of 2.23:1. Age at diagnosis ranged from 1 month to 8 years, with a mean \pm SD of 24 \pm 17.3 months. Fourteen (33.3%) of the cases had a known family history of unexplained deaths, and 9 (9.5%) of the siblings had confirmed OA. In 36 cases (85.7%), parents were consanguineous. Thirty-seven (88.1%) patients had motor delay and 5 (11.9%) had normal motor development, 35 (83.3%) patients had mental delay and 7 (16.7%) had normal mental development.

Glutaric acidemia type 1 was confirmed in 26 (61.9%) followed by methylmalonic acidemia in 7 (16.67%), isovaleric acidemia in 3 (7.14%), propionic acidemia in 3 (7.14%), pyroglutamic acidemia in 2 (4.76%) and D2 hydroxy glutaric acidemia in 1 (2.38%). (Figure 1).

TMS of the included OA cases showed that 2 of the 3 propionic acidemia patients had high C3 in TMS. While 24 (92%) of those with glutaric acidemia type 1, 3 of those with methylmalonic acidemia, all pyroglutamic acidemia, D2 hydroxy glutaric acidemia, and isovaleric acidemia had normal TMS.

Table 1. Initial presentations among our patients

	Number (n=42)	%
Global developmental delay	24	57.1%
Epilepsy	7	16.7%
Vomiting	6	14.3%
Fever-irritability	4	9.6%
Hemiparesis	1	2.4%

Clinical Presentations

The initial presentation among our patients was global developmental delay among 24 (57.1%) patients followed by seizures in 7 (16.7%), vomiting in 6 (14.3%), fever and irritability 4 (9.6%), and hemiparesis in 1 (2.4%). (Table 1).



The age of the 26 patients with glutaric aciduria type 1 at presentation ranged from 5 months to 12 years, with a median age of 37.5 months (mean \pm SD=58 \pm 47months), disturbed conscious level after preceding infection (encephalitic-like picture), macrocephaly, loss of previously acquired skills, and ten patients with extrapyramidal manifestations (dystonia, and abnormal posture) were the clinical presentations in 20 patients. Global developmental delay (GDD) was present in 22 (84.6%) patients and 5(19.2%) patients were suffering from fits.

The median age of the 7 methylmalonic acidemia patients was 5 years (range: 16-117 months) (mean \pm SD: 58.4 \pm 37 months). Four presented clinically by acute decompensation (metabolic acidosis, high anion gap and one had GGD. One presented with acute decompensation with atrophic changes in MRI brain. However, the other 3 had microcephaly GDD (delayed walking and school underachievement), and failure to thrive (FTT), and one of them had generalized tonic clonic epilepsy controlled on 3 anti-epileptic drugs.

Of the 3 patients with propionic acidemia, one patient presented at the age of 4 months with vomiting and fits, the other 2 patients presented at the age of two years, one with acute decompensation and vomiting, and one with GDD.

Of the 3 isovaleric acidemia patients, one patient presented at the age of two years with a diabetic ketoacidosis-like picture (metabolic acidosis, and hyperglycemia), the other patient presented at 5 years with GDD and generalized fits, and the last one presented at 8 years with GDD. Among our 2 pyroglutamic acidemia patients, one patient presented at the age of 10 years with global developmental delay and right-side weakness (hemiparesis). The second patient presented at the age of 2 years with failure to thrive and GDD. The patient with D2-hydroxy glutaric acidemia patient presented at age of 8 months with vomiting and delayed motor and mental development.

MRI brain findings

Abnormal signal in basal ganglion was encountered in 20 (47.6%), followed by cortical atrophy in 11 (26.2%), white matter changes in 11 (26.2%), temporal lobe hypovolemia in 10 (23.8%), ventricular dilatation in 6 (16.7%), arachnoid cyst in 4 (9.5%), normal MRI brain in 3 (7.1%) and encephalomalacia in 2 (4.8%).

Among the 26 patients with glutaric aciduria, the most common radiological finding was increased signal in basal ganglia T2/FLAIR in 11 (42.3%), followed by periventricular white matter changes in 10 (38.50%), temporal lobe hypovolemia in 9 (34.6%), ventricular dilation in 6 (23.1%), arachnoid cyst in 4(15.40%) and cortical atrophy in 4 (15.4%). In only 6 patients with glutaric aciduria type 1 the brain MRI was characteristic with bilateral enlargement of subarachnoid spaces and widening of the Sylvian fissure(14), and this widening was absent the other 20 children with glutaric aciduria.

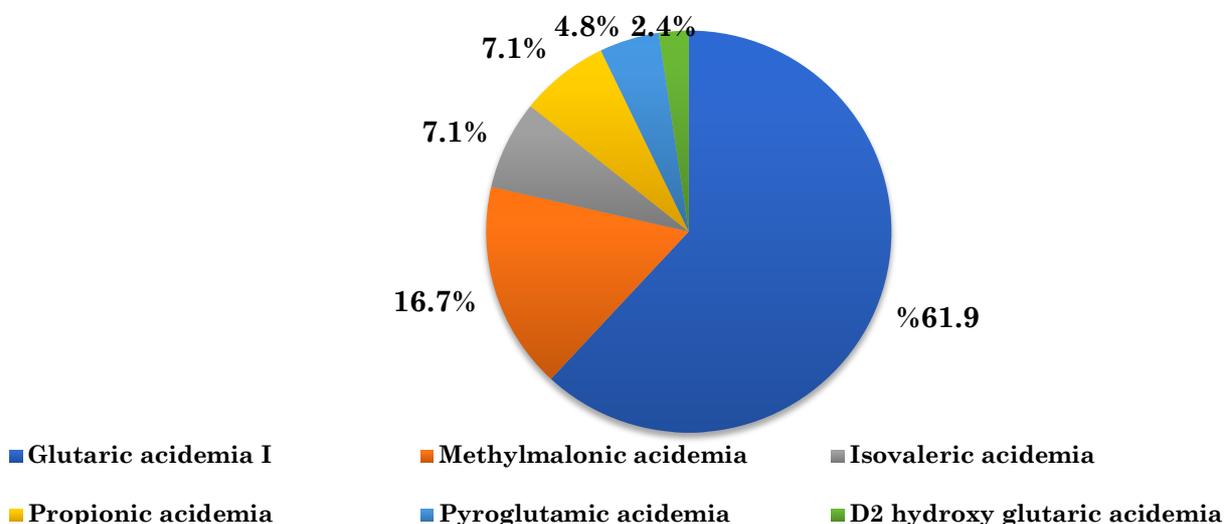


Figure 1. Types and frequency of organic acidemias among our studied cohort.

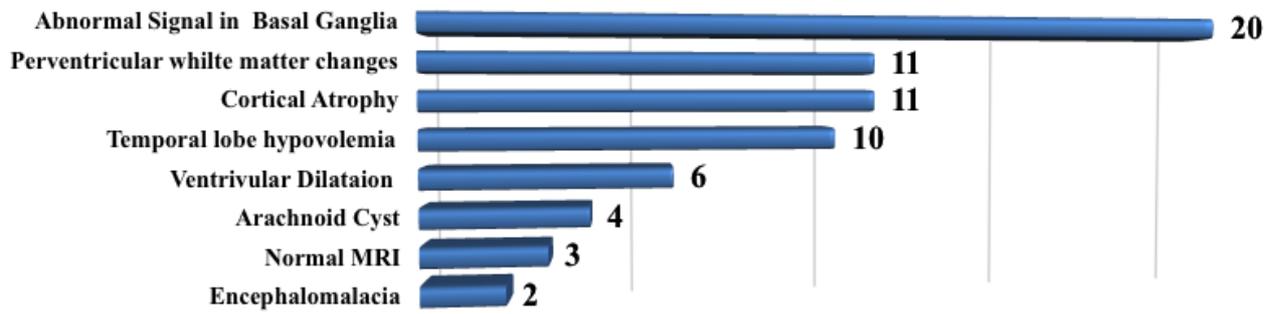


Figure 2. The MRI findings among our studied children with organic acidemia.

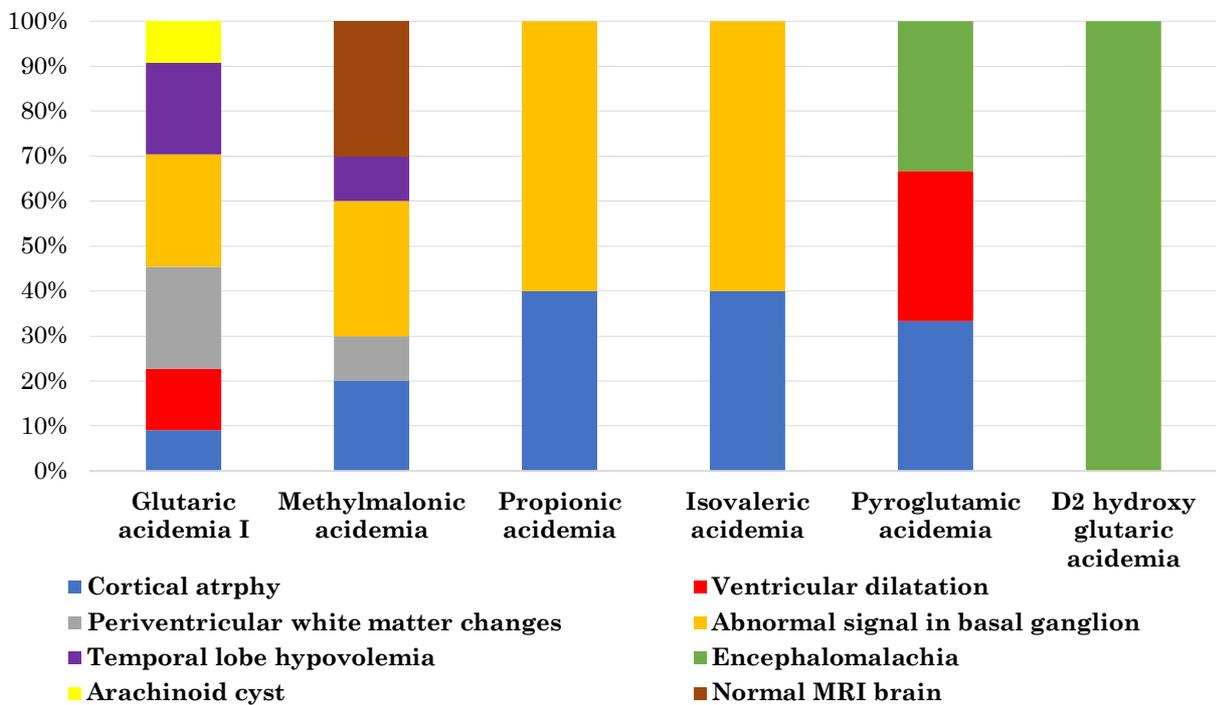


Figure 3. MRI findings in different types of organic acidemias.

The most common radiological finding in the 7 patients with methylmalonic aciduria was an increased signal in basal ganglia in 3 (42.9%), normal MRI brain in 3 (42.9%) followed by cortical atrophy in 2 (28.6%), temporal lobe hypovolemia in 1 (14.3%) and periventricular white matter changes in 1 (14.3%). Increased signal in basal ganglia T2/FLAIR at in 3 (100%) and cortical atrophy at in 2 (66.6 %) were the most common radiological findings in both propionic and isovaleric acidemias. The MRI of the 2 patients with pyroglutamic acidemias was the cortical atrophy, of the left side (hemi-atrophy) in 1, ventricular dilatation and encephalomalacia in 1.

The brain MRI of the infant with D2 hydroxy glutaric acidemia showed areas of encephalomalacia. (Figure 3). The brain MRI among the 7 who suffered methylmalonic acidemia was as follows: One had brain atrophic changes on MRI, 3 had characteristic elevated basal ganglia (globus pallidus) signals on their MRI scans (16), and, the other 3 had normal MRI scans. However, the 3 who had normal brain MRI scans, presented with GDD, FTT, and one of them suffered epilepsy.

Among the 3 with propionic acidemia brain MRI showed increased signals in basal ganglia T2/Flair, and cortical atrophy in two patients. While the MRI in the 3 with isovaleric acidemia showed bilaterally increased signal intensity in basal ganglia in T2/Flair, one with the increased

signal in globus pallidus bilaterally, and the other two signal enhancement was more in the putamen and lentiform nucleus.

MRI in the 2 pyroglutamic acidemia patients was as follows: MRI brain showed cortical atrophy, especially of the left side (hemi-atrophy) with severe left ventricular dilatation in the 10 year-old with right-side weakness (hemiparesis). (Figure 7).

The brain MRI of second patient with FTT and GDD (aged 2 years) showed ventricular dilatation and encephalomalacia. The brain MRI showed areas of encephalomalacia in the infant with D2-hydroxy glutaric acidemia with vomiting and delayed motor and mental development.

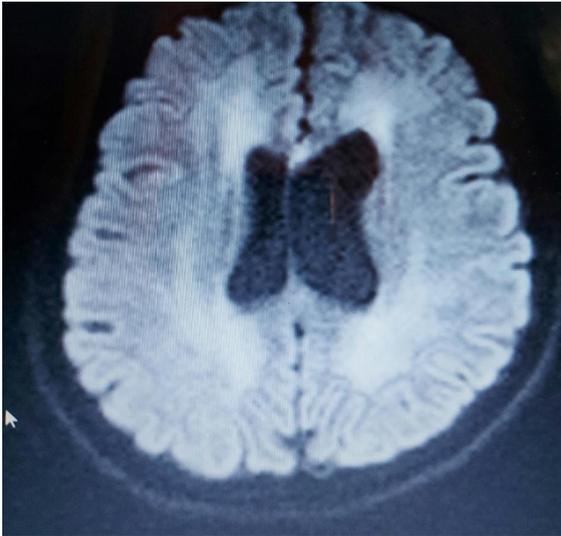


Figure 4. Axial FLAIR MRI brain of a 10 year-old with glutaric aciduria 1 showing asymmetrical ventriculomegaly with altered signal in white matter who presented with global developmental delay, dystonia, failure to thrive, and macrocephaly and was diagnosed at 6 months and on treatment.

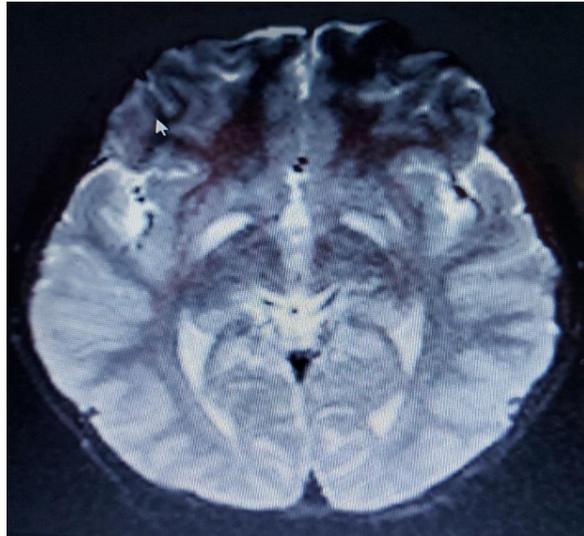


Figure 5. Axial T2 MRI brain of 16 month-old methyl child with malonic aciduria showing temporal lobe hypoplasia, bilateral symmetrical areas of encephalomalacia including 2 globus pallidum and putamen (basal ganglia) and are surrounded by areas of gliosis who presented with mild motor developmental delay.

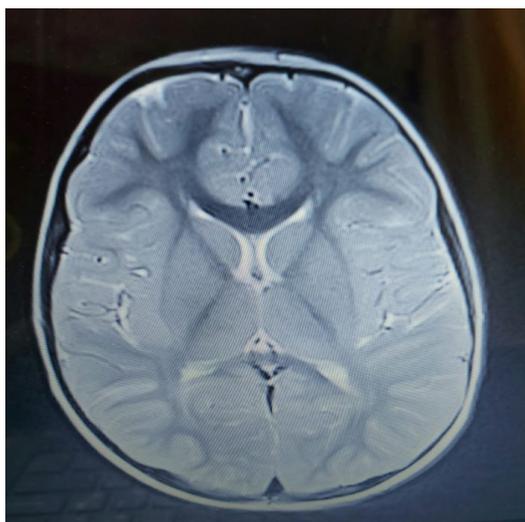


Figure 6. Axial T2 MRI brain of 2 year-old methyl infant with malonic aciduria showing bilateral deep periventricular white matter altered signal mainly occipital who presented with encephalopathy and seizures following viral infection.

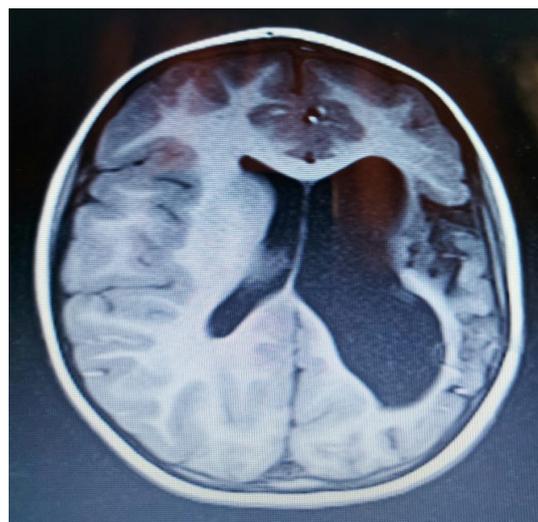


Figure 7. Axial FLAIR MRI brain of 10 year-old child with pyroglutamic acidemia showing left cerebral hemi-atrophy with dilated left lateral ventricle and widened sulci and Sylvian fissure who presented by failure to thrive and global mental and developmental delay.



Discussion

Neonatal screening of OAs affords pre-symptomatic diagnosis before irreversible morbidities and mortality. In Egypt, where neonatal screening program does not include OA, its diagnosis is challenging and relies on high index of suspicion. CNS complications are associated with OA, yet they are not specific or sensitive. Its role is limited to image the extent of macroscopic damage. Routine MRI is limited to detection of macroscopic alterations in brain structure (13). MRI resolution does not detect microstructural neuropathology and does not provide enough functional information of ongoing processes in space and time of brain function and metabolism (12).

The brain imaging by magnetic resonance reveals a plethora of findings. Yet, our work reveals that a normal MRI does not rule out OAs. The abnormal signal of MRI of basal ganglia is not limited to OAs, it was reported to be associated with acidosis irrespective of its etiology (9), kernicterus, mitochondrial disease, perinatal asphyxia (15), gestational alloimmune liver disease, manganese toxicity and others (16). Hence, the abnormal signal of MRI of basal ganglia raises the possibility of the diagnosis of OAs. Yet its value does not exceed that of a meticulous neurologic clinical examination of a neonate or child.

Hence, the definitive diagnosis of OAs rely on biochemical testing as TMS and urine analysis for organic acids. The genotyping was not part of the diagnostic battery of investigations, yet it is essential for family counseling of families with an inflicted child with OA (17). OAs are extremely rare in our experience, yet it is not clear if they are as rare as this study did not address the prevalence or incidence. Again the OAs are notorious of high early life mortality, hence the older our studied children age reflects those who survived.

Our study included 42 children with confirmed OA but we suspect that is an underestimation of the true number of cases of OA, as negative biochemical testing is not against the diagnosis (18). The diagnosis of OAs rely mainly on biochemical analysis. Yet, biochemical analysis also has its limitations. The diagnostic sensitivity of organic acid tests can vary according to the clinical condition of the child, whether the sample was collected during an asymptomatic or decompensation phase (18). An organic acid profile is positive during an intercurrent illnesses of the child with OA; however, this test has several shortcomings. In illnesses where the excretion of diagnostic metabolites is a reflection of the residual activity of the defective enzyme, the dietary load of precursors, and the anabolic/catabolic status of the patient, informative profiles may not always be found. For example, some people with glutaric acidemia type I are referred to be "low excretors" because their levels of 3-hydroxyglutaric acid and glutaric acid in the urine may not be noticeably abnormal (19). As a result, in some cases, it may be necessary to specifically quantify certain metabolites in other physiologic fluids (such as cerebrospinal fluid, amniotic fluid, plasma or serum) in order to shed light on an ambiguous result of organic acids in urine analysis. Confirmatory testing is always advised as a tissue biopsy, in vitro- enzyme assay, molecular analysis of blood cells or cultured cells.

The age of our studied cohort reflects the older age at diagnosis. The late diagnosis often followed misdiagnosis as a high proportion of them were initially diagnosed as having septicemia or meningitis or even dying before taking the biochemical samples. The delay in diagnosis resulted in significant morbidity, such as mental retardation and physical handicaps, among survivors in this study.

The need for the early pre-symptomatic diagnosis is precluded in countries where the neonatal screening programs for OAs exist. OAs cause serious morbidity, brain damage, with a huge financial and social burden. Their diagnosis in countries where neonatal screening is not the rule, is delayed, and relies upon clinical examination and biochemical testing (6).

Conclusion

Abnormalities on brain MRI are common but not unique in organic acidemias or its types, and are not sensitive or specific. Normal brain MRI does not exclude the diagnosis of OAs. Neonatal screening is a necessity to detect the organic acidemias before the irreversible brain damage.



Author Contributions:

All authors contributed to the study conception and design. All read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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