Magnetic resonance imaging of the brain in the diagnostic evaluation of microcephaly

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Abstract: Microcephaly is defined as small head size characterized by occipito-frontal circumference (OFC) at least 2 standard deviations (SD) below the mean for age and sex. Microcephaly is associated with numerous disorders of diverse etiology. Radiology plays a fundamental role in determining the etiology. MRI is often the imaging modality of choice. **Aim of the work:** To assess the contribution of brain magnetic resonance imaging (MRI) in establishing an etiological diagnosis in children presenting with microcephaly in the first two years of life. **Methods**: Nine hundred Egyptian patients attending the general pediatric and neurology clinic of Benha University Hospital (BUH) and clinic of inherited metabolic disorder at the centre of social and preventive medicine of Cairo University Children Hospital (CUCH) were screened for microcephaly. This was done by measuring the **(**OFC**),** and then MRI was performed to all microcephalic patients. Other investigations done according to the condition. **Results:** Fifty five patients out of 900 cases were microcephalic, below the 3rd percentile of Egyption charts. Male and female distribution was 31 (56.4%) and 24 (43.6%) with ratio of 3:2.The ages of presentation ranged from 2 months to 84 months with mean age of 20.6 ± 15.6 months. All patients were symptomatizing before 24 months with mean age of (6.5 ± 4.2 months). The patients were classified according to the final diagnosis into 3 groups: primary microcephaly 11cases (20%), secondary microcephaly 29 cases (52.72%) and undiagnosed cases 15 cases (27.28%). The most frequent MRI finding is brain atrophy in 11(20%) cases followed by demylination in 10(18.18%) cases, leukomalecia &atrophy in 7(12.7%) cases, demylination &atrophy in 6(10.9%) cases, basal ganglia lesion in 5(9%) cases, congenital brain malformations in 4(7.3%) cases, microcephalic changes in 3(5.5%) cases and leukomalecia only in 2(3.6%) cases. **Conclusion:** MRI is considered as a golden standard in the evaluation of brain abnormalities in patients with microcephaly**.** It is diagnostic in congenital brain malformations and in combination with history & clinical findings, it can suspect the diagnosis, as in ARM, Leigh syndrome & HIE cases or point to specific test for diagnosis as in MLD & PKU.

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1. Introduction

Microcephaly is an important neurologic sign and is usually defined as a head circumference (HC) more than 2 SDs below the mean for age and gender (1). Microcephaly may be described as primary and secondary. Primary microcephaly in which the brain fails to grow to the correct size during pregnancy (2). Secondary (also known as acquired) microcephaly is a condition in which a child's head circumference is within the normal range at birth and for an undefined period thereafter, but then does not increase as fast as normal and, as a result, crosses percentiles to below the second percentile (3). It is important to measure a patient's head circumference at birth. Serial head circumference measurements are more meaningful than a single determination, particularly when the abnormality is minimal (4). The assessment of microcephaly is both clinical and radiological (5). Microcephaly has been associated with numerous genetic etiologies and because the genetics of microcephaly is a rapidly evolving field, currently available data likely underestimate the importance and relevance of genetic testing as part of the diagnostic evaluation of children with microcephaly (6). Many of the microcephaly genes identified to date have been associated with specific phenotypes, allowing more targeted clinical testing. Available screening tests for chromosomal deletions and duplications include karyotyping, subtelomeric fluorescent in situ hybridization, and bacterial artificial chromosome or oligo-based comparative genomic hybridization (7).

Investigations of microcephaly requires a systematic consideration of each of the etiologic causes, search for risk factors in the mother , details of pregnancy, birth , developmental progress and a detailed family history (8). MRI is considered as a golden standard in the diagnosis of microcephaly as it often reveals findings that are more difficult to visualize on CT, such as migrational disorders, callosal malformations, structural abnormalities and disorders of myelination (9). Advances in neuroimaging and genetics have improved understanding of the causes of microcephaly, suggesting new approaches to classification and testing(2). Once the cause of

microcephaly has been established, the physician must provide accurate and supportive genetic and family counseling. Because many children with microcephaly are also mentally retarded, the physician must assist with placement in an appropriate program that will provide for maximum development of the child (10). The present study aims to assess the contribution of brain magnetic resonance imaging (MRI) in establishing an etiological diagnosis in children presenting with microcephaly in the first two years of life.

2. Subjects and Methods:

Subject selection

Among 900 patients referred from the general pediatric and neurology clinic of Benha University Hospital (BUH) and clinic of inherited metabolic disorders at the centre of social and preventive medicine of Cairo University Children Hospital (CUCH). Fifty five patients were found to be microcephalic according to Egyption charts of *Ghaly et al., (2002)(11).* This study was conducted in the period of March 2009 to September 2009.

Inclusion criteria:

Our subjects were patients presenting with microcephaly before the age of 2 years.

Methods

- **History:**Full history taking was obtained from all cases including: Personal history , Present history ,Developmental history , Perinatal history and Family history including family pedigree analysis

§ **Examination:**

General Examination:

All cases were subjected to general examination including anthropometric measures (head circumference, height and weight) using Egyptian growth charts 2002.

Local Examination:

Our patients were subjected to neurological examination including motor power, tone and reflexes (deep &superficial), any abnormal movement and cranial nerves examination**.**

§ **Investigations:**

Radiological Investigations: MRI was used for all cases of the study: It was performed on 1.0 Tesla unit (Signa, GE, Milwaukee) using a head coil. Some MR examinations were performed on 1.0 Tesla (Gyroscan NT 10; Philips Medical systems). MR examinations, using head coil, included; Axial and coronal T2 FSE using 2000-5000/98-120 TR msce/TE msec, one to four signals acquired, 16-22 cm FOV with or without a rectangular Field, 192-256 x 256 matrix, 3-5 mm thick sections with 0.3-0.5 mm intersection gap. Axial TI wighted images were obtained using 400-650/20-30 TR msec/TE msec, 2-4 signals acquired, 128-192 x 256 matrix, 16-22 cm FOV, and 3-5 mm thick contiguous sections. Sagital TI WSE MR imaging (400-700/11-20. 1-2 signals aquired, 128-192 x 256 matrix, 20-40 cm FOV, 5 mm thick sections with 0-2.5 mm intersection gap. Additional coronal TI WES was obtained using the same parameters used for axial TI. Axial T2 FLAIR (Fluid attenuated inversion recovery) images were done using 10,000/140/2,200 TR msec/echo time msec/inversion time msec, one signal acquired, 20-22 cm FOV, 192x256 matrix, 4-5 mm thick sections with 1.0-2.5 mm intersection gap.

Laboratory investigations:

Basic metabolic investigations were done to all patients including:

§ Complete blood picture, random blood sugar, liver function tests, kidney function tests, arterial blood gases, and anion gap calculation in cases of metabolic acidosis.

§ Serum ammonia & lactate, urine ketones and reducing substances.

Specific metabolic investigations:

§ TMS: tandem mass spectrometry, using MS/MS laboratory method, which is a technique that allows the screening of multiple disorders in the same blood spot collected on the standard card. More than 20 preventable genetic disorders can be screened by blood drop**.**

§ Organic acids profile in urine using Gas chromatography mass spectrometry (GC/MS) was performed for patients with abnormal acylcarnitine profile or those with unexplained mental retardation or compensated metabolic acidosis. This qualitative urinary organic acid method is capable of detecting over 200 organic acids for a large numbre of metabolic conditions.

§ Definitive diagnosis by enzymatic analysis was done in some cases such as Aryl sulphatase An in MLD (Metachromatic Leuko Dystrophy).

§ Other metabolic investigations: Pyruvate, VLCFA (very long chain fatty acid): for suspected perioxosomal disorders.

I.Q (Intelligence Quotient), TORCH screening & karyotyping needed in some cases accordingly. Other studies as (FISH for William) which done in cases suspected to be syndromatic.

Neurophysiologic study

ERG, VEP, Fundus examination, ABR, EEG, EMG and Echocardiography were carried out.

3. Results

Our results revealed that, out of 900 patients attending the neuropediatric clinic, 55 (6.11%) patients were found to be microcephalic**.** Male and female distribution among the study group was 31 (56.4%) and 24 (43.6%) with ratio of 3:2.

The ages of presentation ranged from (2 months to 84 months) with mean age of 20.6 ± 15.6 months. However, all patients were symptomatizing before 24 months with mean age of 6.5 ± 4.2 months .The 55 patients of the study were classified according to their final diagnosis into 3 groups; Group1: primary microcephaly 11 patients (20%), Group Ц secondary microcephaly 29 patients (52.72%) and Group Ш undiagnosed group 15 patients (27.28%) . Group1 subclassified into: genetic; (9.1%), syndromatic; (3.6%) and congenital brain malformations (7.2%). Group Ц sub-classified into: perinatal causes (HIE) or cerebral palsy group; 12 cases (21.81%), neuro-metabolic; 10 cases (18.18%) including aminoacidopathy (PKU and homocystinuria) and organic aciduria (MMA **2**cases and 3-MCG **1**case), neurodegenerative; 3 cases (5.45%) including 2 cases MLD and 1 case of Rett syndrome and mitochondrial disorders (Leigh syndrome) 4 cases (7.27%).

Table (1) demonstrates the clinical manifestations of the studied groups. The most prevalent clinical manifestation was developmental delay in all cases 55 (100%), followed by tone abnormality in 46/55cases (83.63%). The dysmorphic features were detected in 22/55 (40%). Abnormal movements in 15/55 (27.27%). Eye affection was found in 6 cases **(**10.91%) followed by hearing affection in 3 cases (5.45%). Associated anomalies and speech affection (dysartheria) were detected in 2 (3.64%) cases each. The most frequent history findings were positive consanguinity in 35 cases (63.63%) and seizures in 27cases (49.09%). Table 3 shows analysis of clinical presentation of 40 diagnosed cases. MRI findings in all the cases (table 3)reveals that, the most frequent MRI finding is brain atrophy in 11(20%) cases followed by demylination in 10(18.18%) cases, leukomalecia & atrophy in 7(12.7%) cases, demylination &atrophy in 6(10.9%) cases, basal ganglia lesion in 5(9%) cases, congenital brain malformations in 4(7.3%) cases, microcephalic changes in 3(5.5%) cases and leukomalecia only in 2(3.6%) cases.

MRI of Autosomal Recessive Microcephaly is shown in figure (1). MRI of Congenital Brain Malformation (Cortical dysplasia and incomplete lissencephaly) is shown in figure (2). MRI of Hypoxic ischemic Encephalopathy is shown in figure (3). MRI of Aminoacidopathy (PKU) is shown in figure (4). MRI of Methylmalonic academia (MMA) shown in figure (5). MRI of Metachromatic leukodystrophy is shown in figure (6). MRI of Rett syndrome is shown in figure (7). MRI of Leigh syndrome is shown in figure (8).

Table (1): Clinical manifestations in the study groups.

Clinical manifestation	number	%
Positive Consanguinity	35	63.63%
Abortion	17	30.90%
Sibs death	12	21.82%
Other sibs affection	17	30.90%
Family history of Similar condition, other neurological disorder or mental retardation.	15	27.27%
Maternal illness	9	16.36%
History of DCL(disturbed conscious level)	2	3.64%
Seizure	27	49.09%
Abnormal movements	15	27.27%
Hypertonia **Hypotonia** **Normotonia**	27 19 9	49.09% 34.54% 16.36%
Developmental delay **Motor delay** **Mental delay** **GDD(Global developmental delay)** **Regression**	***55*** 9 3 36 7	***100%*** 16.36% 5.45% 65.45% 12.73%
Dysmorphic feature	22	40%
Associated anomalies	2	3.64%
Eye affection **albinotic fundus (3cases) 5.45%** **pallor of optic disc (2cases) 3.64%** **high myopic (1case) 1.81%**	6	10.91%
Hearing affection	3	5.45%
Speech affection (dysartheria)	2	3.64%

Table (2): Distribution of patients of the study groups according to their final diagnosis.

	Final diagnosis	**Number (%)**
Primary microcephaly 11/55 (20%)	**1-Autosomal Recessive microcephaly**	**5/55(9.09%)**
	2- Syndromatic	**2/55(3.63 %)**
	-Cornelia de lange syndrome	1/55(1.81%)
	-Smith lemli opitz syndrome	1/55(1.81%)
	3-Congenital brain malformations	**4/55(7.27%)**
	-Pachygyria	2/55(3.63%)
	-Lissencephaly	1/55(1.81%)
	-Cortical dysplasia and incomplete lissencephaly	1/55(1.81%)
Secondary microcephaly 29/55 (52.72%)	**1-(HIE)**hypoxic ischemic encephalopathy	**12/55(21.81%)**
	2- Neurometabolic	**10/55(18.18%)**
	a)Aminoacidopathy	**7/55(12.72)**
	-PKU(phenyl ketonuria)	6/55(10.9%)
	-Homocystinuria	1/55(1.81%)
	b)- Organic aciduria	**3/55(5.45%)**
	-MMA(methyl malonic acidemia)	2/55(3.63%)
	-MCG(Methyl crotonyl glycinuria)	1/55(1.81%)
	3-Neurodegenerative	**3/55(5.45%)**
	- MLD (metachromatic leukodystrophy)	2/55(3.63%)
	- Rett syndrome	1/55(1.81%)
	4-Leigh syndrome	**4/55(7.27%)**
Undiagnosed cases 15/55 (27.28%)		**15/55(27.28%)**
Total number (%)		**55(100%)**

Table (3): Analysis of clinical presentations of diagnosed cases (40cases)

clasification	sub clasification	Final Diagnosis	Consanguinity	Abortion	Sibs death	Other sibs affection	1-disturbed conscious level 2-seizure(s)	Dysmorphic features	Tone			Developmental Delay				Vision affection	Hearing affection	Speach affection
									spasticity	Hypotonia	Normotonia	Motor	Mental	Regression	Global developmental delay(GDD)			
Secondary Microcephaly / Primary Microcephaly	1- Genetic	ARM* 5 (9.09%)	+ve (3)			+ve		+ve			+ve		+ve (3)		+ve (2)			+ve (1)
	2-Syndromatic	CDS*1 1 (1.81%)	+ve					+ve							+ve			
		SLOs*2 1 (1.81%)	+ve	+ve			s+ve	+ve							+ve			
	3-Congenital brain malformations	Pachygyria 2 (3063%)	+ve (1)	+ve (2)			s+ve (2)		+ve (2)						+ve		+ve (1)	
		Lissencephaly 1(1.81%)	+ve	+ve			s+ve		+ve						+ve			
		Corticaldysplesia+Lissencephay1 (1.81%)		+ve			s+ve	+ve	+ve						+ve			
	1-P	HIE*3 12 (21.8%)	+ve (6)	+ve (3)	+ve (2)		s+ve (11)	+ve	+ve (11)	+ve (1)		+ve (9)			+ve (3)	+ve (2)		
	2-Neuro-metabolic / a-Amino acidopathy	P KU*4 6(10.9%)	+ve (4)	+ve (2)	+ve (1)	+ve (6)	s+ve	+ve	+ve (4)		+ve (2)				+ve			
		Homc*5 1(1.81%)					s+ve			+ve					+ve			
	2-Neuro-metabolic / b-Organic aciduria	MMA*6 2 (3.63%)	+ve (2)			+ve (1)	DCL (2)		+ve (1)		+ve (1)				+ve			
		3MCG*7 1(1.8%)	+ve				DCL (1)		+ve						+ve			
	3- neuron-degenerative	MLD*8 2(3.63%)	+ve (1)	+ve	+ve (1)				+ve					+ve	+ve			
		Rett syndrome 1(1.81%)	+ve	+ve				+ve	+ve					+ve	+ve			+ve (1)
	4- Mitochondrial	Leigh syndrome 4(7.27%)	+ve (3)	+ve			s+ve (2)		+ve (1)	+ve (3)				+ve	+ve			

*Autosomal Recessive microcephaly,*1 Cornelia de lange syndrome, *2 Smith lemli opitz syndrome , *3 hypoxic ischemic encephalopathy , *4 phenyl ketonuria ,*5 Homocystinuria ,*6 methyl malonic acidemia , *7 Methyl crotonyl glycinuria , *8 metachromatic leukodystrophy.

Table (4): MRI findings of all cases of the study group

CLASSIFICATION	sub classifications	Final Diagnosis		Microcephalic changes	Brain atrophy	Leukomalecia	Leukomalecia/ Atrophy	Demylination	Demylination/ Atrophy	Congenital brain Mal formation	Basal Ganglia lesion	Others
Primary microcephaly	1-Genetic	Autosomal recessive microcephaly(ARM)5 (9.09%)		3	1							Colpocephaly&Interhemispheric cyst.
	2-Syndrometic matic	Cornelia de lange Syndrome (CDLS)1(1.81%)			1							
		Smith lemli Opitze Syndrome (SLOS)1(1.81%)										Incomplete agenesis of corpus callosum.
	3-Congenital brain Mal formations	Pachygyria2(3.63%)								2		
		Lissencephaly1(1.81%)								1		
		Cortical dysplesia & incomplete Lissencephaly1(1.81%)								1		
Secondary Microcephaly	1-Perin atal		Hypoxic ischemic encephalopathy (HIE)12 (21.81%)		3	2	7					
	2-Neuro metabolic	a- Amino acidopathy	(PKU) Phenyl Ketonuria6 (10.9%)					2	4			
			Homcystinura 1(1.81%)					1				
		b- Organic acidduria	(MMA) Meth-yl Malonic Acidemia 2 (3.63%)					1			1	
			(3-MCG) 3-Methyl crotonyl glycinuria1(1.81%)		1							
	3- neurodegenerative	Metachromatic leukodyst – rophy (MLD) 2(3.63%)						2				
		Rett syndrome 1(1.81%)			1							
	4- Mitoch Ondrial	Leigh syndrome 4(7.27%)									4	
undiagnosd	? Mitochondrial				3				2			2 Normal
	? Neurodegenerative							4				
	? Syndromatic				1							3 Normal

Autosomal Recessive Microcephaly

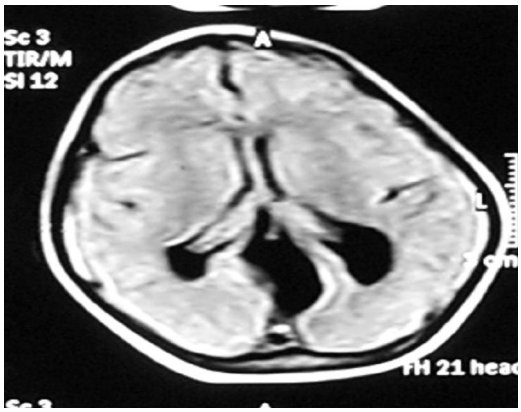


Fig (1) MRI axial section showing; Microcephaly, Trigonocephaly,colpocephaly and inter- hemispheric cyst and abnormal gyral pattern.

Congenital Brain Malformation (Cortical dysplasia and incomplete lissencephaly)

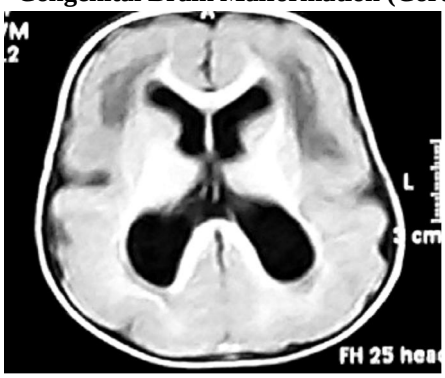


Figure 2 (a)

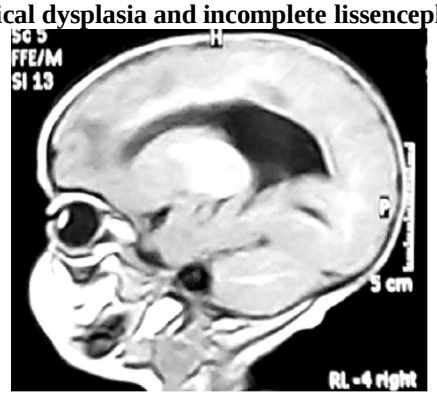


Figure 2 (b)

Figure 2 (a,b) : MRI brain T1WI Axial (a) and Sagittal (b) sections of female patient aged 6 month showing cortical dysplasia(thickening) with lissencephaly (incomplete type) , due to the presence of a smooth brain surface with shallow Sylvain fissure and some gyral formation

HIE (Hypoxic ischemic Encephalopathy)

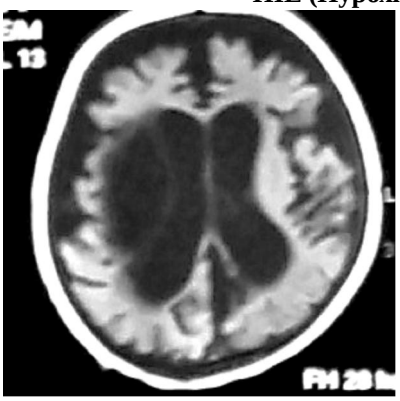


Figure 3 (a)

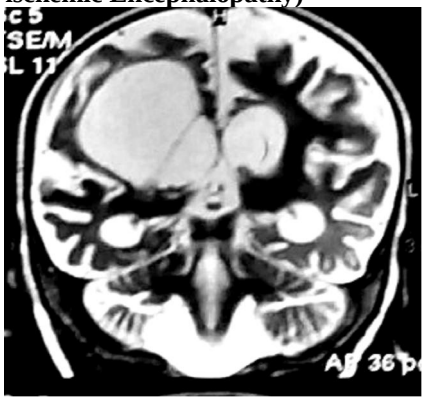


Figure 3 (b)

Figure 3 (a,b): MRI brain Axial T1WI (4a) and Coronal T2WI (4b) , sections of HIE male patient aged 1 year showing oblong shape cystic encephalomalecia (6x3 cm) with in the right deep partial periventricular region, brain atrophy appears as (dilated ventricles) central atrophy and (deep sylvian fissure and prominent sulci) peripheral atrophy.

Aminoacidopathy, Phenyl Ketonuria(PKU)

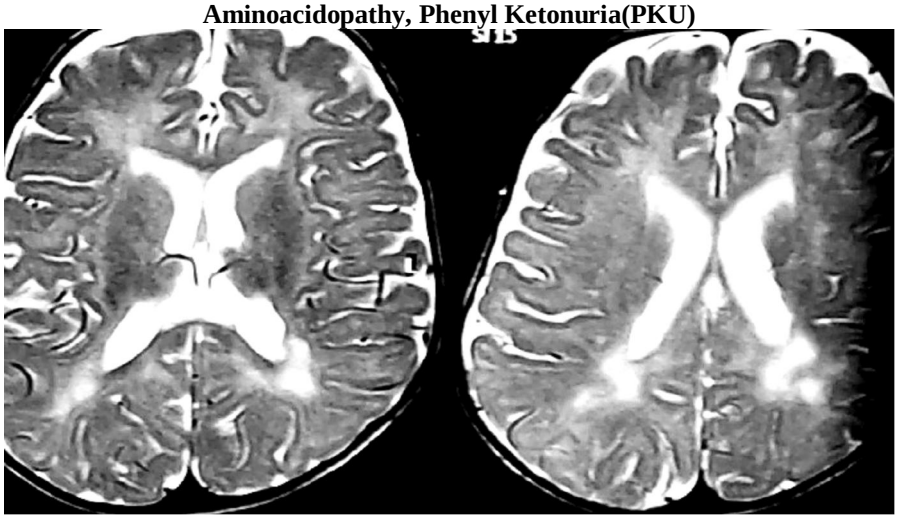


Figure 4 (a)

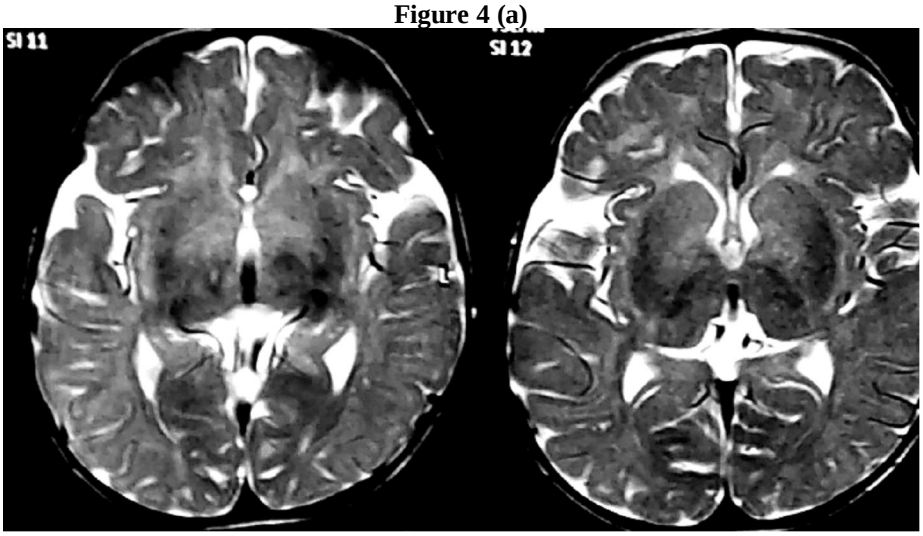


Figure 4 (b)

Figure 4 (a,b) : MRI brain Axial sections T2WI of PKU female patient aged 16 month. (a) Showing defective mylination of the white matter appears mainly priventricular (b) showing cerebral atrophy appears as (dilated ventricles) central atrophy and (deep sylvian fissure and prominent sulci) peripheral atrophy .

MMA (Methyl Malonic Academia)

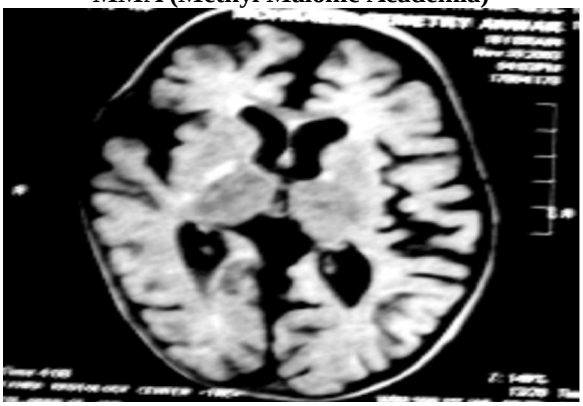


Figure 5: MRI brain Axial section FLAIR of male patient aged 18 month, proved to be MMA, showing diffuse high signal intensity lesion involving the white matter bilaterally with central and cortical atrophy.

Metachromatic Leukodystrophy (MLD)

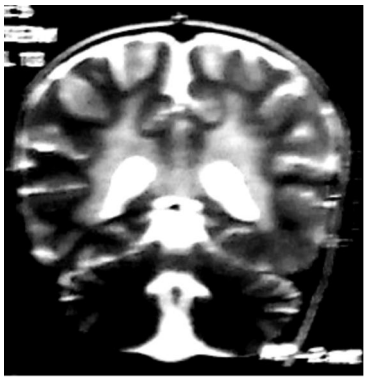


Figure 6(a)

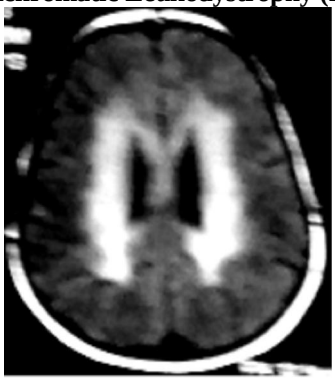


Figure 6(b)

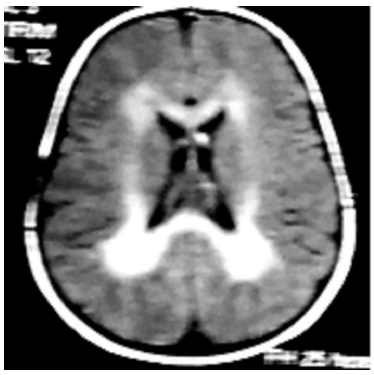


Figure 6(c)

Figure 6 (a,b,c) : MRI brain coronal (a) , axial (b,c) flair sections of female patient aged 2 years diagnosed as MLD showing diffuse high signal intensity lesion involving the periventricular white matter mostly peritrigonal , forceps major and minor sparing the sub cortical u fibers , basal ganglia , thalamus and the posterior fossa.

Metachromatic Leukodystrophy (MLD)

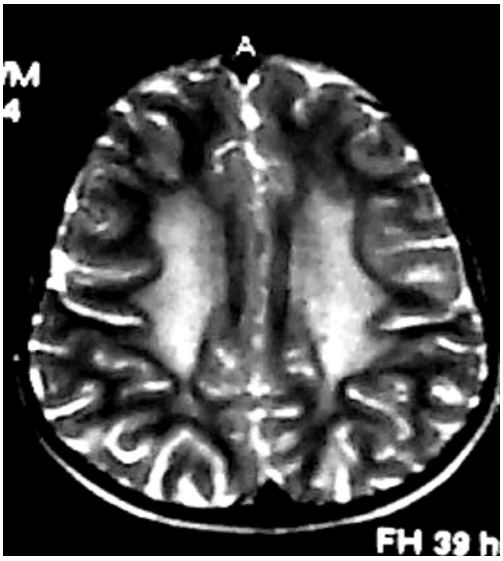
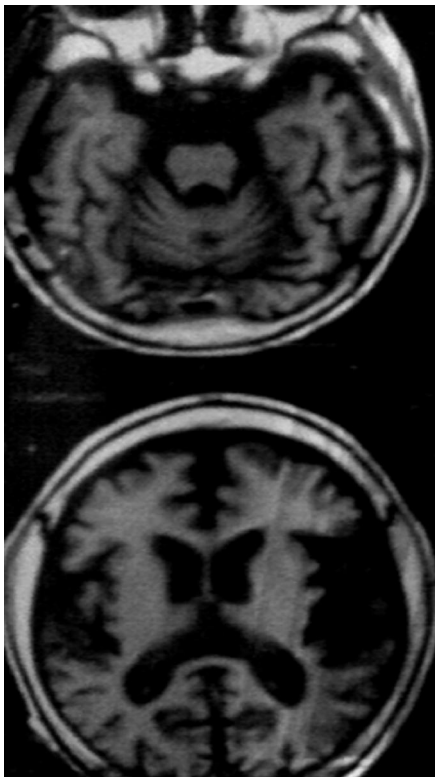


Figure 6 (d): MRI brain axial (d) T2 WI of the same patient showing centrum semi oval with leopard appearance**.**

(Rett syndrome) Cerebral and cerebellar atrophy



Figure(7) : MRI brain Axial sections T1WI of female patient aged 3 years diagnosed as Rett syndrome showing cerebellar atrophy and cerebral atrophy appears as (dilated ventricles)central atrophy and (deep sylvian fissure and prominent sulci)→ peripheral atrophy

Leigh syndrome

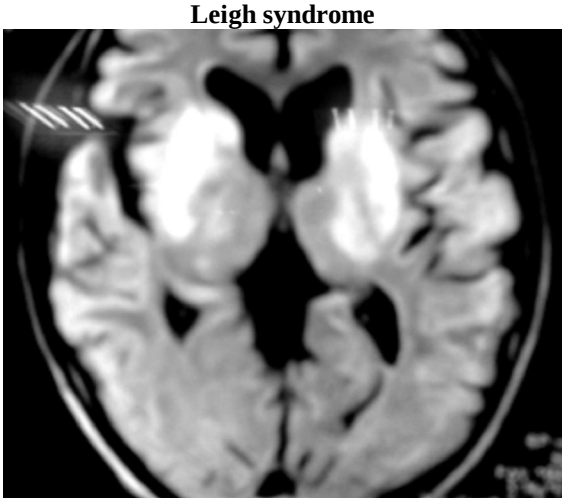


Fig (8) : Brain MRI axial section FLAIR of patient aged 1 year diagnosed as Leigh syndrome showing bilateral affection of basal ganglia which shown as high signal intensity in lentiform , caudate and thalamus.

4. Discussions

The yield of neuro imaging in microcephaly ranges from 43% to 80% in many studies *(2).* The yield of neuroimaging in the current study is 72.72%.We found that secondary microcephaly is the most frequent type, the same was reported by Peter et al., (3). Coexistent conditions with microcephaly include epilepsy (40%), cerebral palsy (20%), mental retardation (50%), and ophthalmologic disorders (20% to 50%) (*2).*These disorders are comparable to our results as we found epilepsy in(50%), cerebral palsy in(21%),GDD in (65%) and ophthalmologic disorders in (11%). The usefulness of MRI is apparent as certain malformations (e.g., lissencephaly, schizencephaly) are well known to be associated with severe neurologic impairment and specific gene abnormalities have been found in several of these disorders(*2*). The current study showed that all cases with congenital brain malformations had microcephaly since birth, hypertonia, hyperreflexia, seizures and GDD. This is in accordance with *Herman & siegel (12) and Poirier et al., (13).* Our patients with pachygyria had MRI findings of large gyri, few sulci and thick cortex on both cerebral hemispheres. Those with lissencephally had MRI findings of agyri, thickened cortex, straight grey white matter and shallow sylvian fissure. This is in accordance with *Barkovich &Raybaud (14)).* Cortical dysplasia and incomplete lissencephally was diagnosed when MRI showed abnormal cortical thickening, incomplete lissencephally & periventricular abnormal signals and this is in agreement with *Abdel Razek et al., (15).*

Microcephaly has been associated with numerous genetic etiologies, including syndromes *as* Angelman, Cornelia de lange and Smith lemli opitz *(6).* Cornelia de lange , Smith lemli opitz ,Leigh and Rett syndromes were diagnosed among our cases. The current study revealed (ARM) in (9%) of cases, while other studies by *Barkovich et al., (16)* and *Wycliffe et al., (9)* reported higher incidence of (ARM) 15.5% to 53.3%, and this may be explained by, the unfeasibility of molecular genetics to diagnose more cases. The diagnosis of (ARM) in our patients was based mainly on the presence of dysmorphic facial features, mental retardation coupled by MRI findings of microcephalic changes (small cerebral hemispheres, shallow sylvain fissure and simplified gyral pattern), this is in agreement with *Rajab et al.,* (17). Despite advances in medical and technological possibilities, perinatal asphyxia is still a matter of concern due to its considerably high rate of mortality and morbidity *(18).* Twelve cases (21.81%) were diagnosed as HIE or cerebral palsy , they presented with microcephaly, motor delay mainly, history of perinatal problem especially during delivery which required NICU admission after delivery(7 cases) and a static course since birth, these clinical criteria are in agreement with *Adcock& Papile (19).*In this group , seizures appeared to be the most common feature (11/12) cases, the same found by *Hahn &Olsan(20).*The main MRI findings in this group were atrophy (central & cortical) in 3/12cases, Peri ventricular leukomalecia in 2/12 cases and both in 7/12cases, so 9/12 cases (75%)of HIE cases demonstrated PVL on MRI. Valeo & Tom (21), reported that MRI findings of 351 of children with CP showed that more than 42 percent had damage to white matter and nearly 90 percent of the children scanned displayed cerebral pathology, including basal ganglia, cortical and subcortical areas, as well as malformations, and infarcts, they concluded that MRI is an important diagnostic tool in cerebral palsy. Metabolic disorders are more likely to cause postnatal onset microcephaly and are typically associated with global developmental delay (GDD). The prevalence of metabolic disorders among children with microcephaly is 1% to 5% *(22).*The current study revealed metabolic disorders in 10 (18.18%) patients, this large number in relation to other studies, could be attributed to the large percent (63.63%)of consanguineous marriages found in our study. The yield of metabolic testing in microcephaly is higher when a parental history of consanguinity is present *(23).* In the current study, patients diagnosed as PKU presented with microcephaly, MR, positive history of consanguinity, fair complexion, agitated behavior, GDD and convulsion in some cases. MRI findings of PKU cases showed demylination in the periventricular area with central and cortical atrophy, this is in agreement with *Harald et al., (23) and Hahnel (24).* Two of our cases were diagnosed as (MMA), they presented with history of coma and admission to ICU,

microcephaly, myoclonic seizures and GDD. Laboratory findings in MMA were metabolic acidosis, increased C3 by (Ms/Ms), methylmalonic, methylcitrate and hydroxy propionic acid in organic acid profile,this is in agreement with *Radmanesh et al. (25).*MRI findings of MMA cases showed bilateral diffuse abnormal signals intensity in the white matter in one case and bilateral affection of both globus pallidus(GP) in the other one, and this is in agreement with *Girgis et al.,(26).*

MRI findings in cases of MLD show diffuse high signals involving periventricular white matter bilaterally and sparing the sub cortical U fibers, basal ganglia and thalami .The posterior fossa and the centrum semiovale show leopard skin appearance, the same reported by *Kim et al., (27).*

Leigh syndrome diagnosed in 7.27% of our cases (4/55). The main clinical manifestations were microcephaly, history of developmental regression, hypotonia, dystonia, metabolic acidosis and high lactate level. MRI findings in this group revealed basal ganglia affection. AL Kartikasalwah &LH Ngu (28) in their study on Leigh syndrome ,reported that, the symmetrical necrotic lesions in the basal ganglia and/or brainstem which appear as hyperintense lesions on T2-weighted MRI is characteristic and one of the essential diagnostic criteria, together with neurological problems should prompt the clinician to investigate for Leigh syndrome. In our study, the case diagnosed as Rett syndrome presented with microcephaly, history of regression and GDD, non purposeful hand movements and autistic behavior. This is in agreement with Moog et al., (29). MRI findings of this case demonstrated, cerebral and cerebellar atrophy and this is in agreement with Carter (30).

5. Conclusion

MRI is considered as a golden standard in the evaluation of brain abnormaities in patients with microcephaly**.** It is diagnostic in congenital brain malformations and in combination with history & clinical findings, it can suspect the diagnosis, as in ARM, Leigh syndrome & HIE cases or point to specific test for diagnosis as in MLD & PKU.

Abbreviation: HIE (hypoxic ischemic encephalopathy)- HC (head circumference)- TMS (tandem mass spectrometry) –PKU (phenylketonuria) - MLD (Metachromatic leukodystrophy) –ERG (electroretinogram) –VEP (Visual evoked potentials) – ABR (auditory brain stem)

References

1. Woods C. Human microcephaly. Curr Opin Neurobiol 2004;14: 112–117.
2. Ashwal S, David M, Lauren P, and William B: Evaluation of the child with microcephaly (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2009; 73; 887-897
3. Peter Stuart Baxter, Alan Steven Rigby, Marianne Hélène et al.,. Acquired Microcephaly: Causes, Patterns, Motor and IQ Effects, and Associated Growth Changes. PEDIATRICS Vol. 124 No. 2 August 2009, pp. 590-595.
4. Robert D.: Oro-facial-digital syndrome IX with severe microcephaly: A new variant in a genetically isolated population. American Journal of Medical Genetics Part A Special Issue: M. Michael Cohen Jr. Festschrift 2007; 143A, Issue 24, pages 3309–3313,
5. Russell SA, McHugo J, Pilling D. Cranial abnormalities. In: Twining P, McHugo J, Pilling D (eds) Textbook of fetal abnormalities. Churchill Livingstone, Edinburgh.2007; pp 95–141.
6. Mochida GH, Walsh CA. Molecular genetics of human microcephaly. Curr Opin Neurol 2001; 14:151–156.CrossRefMedline
7. Abuelo D. Microcephaly syndromes. Semin Pediatr Neurol 2007; 14:118–127.
8. Bale S, Amos C, Parry D and Bale A. The relationship between head circumference and height in normal adults and in the nevoid basal cell carcinoma syndrome and neurofibromatosis type 1. Am J Med Genet 1991; 40: 206-210.
9. Wycliffe ND, Thompson JR, Holshouser BA, Ashwal S. Pediatric neuroimaging. In: Swaiman KF, Ashwal S, Ferriero DM. Pediatric Neurology Principles & Practice, Fourth edition. Philadelphia: Mosby Elsevier; 2006
10. Haslam R. Microcephaly. In: Oxford Desk Reference: Clinical Genetics, 1st ed. Oxford University Press, Oxford 2007. p. 172.
11. Ghaly Isis, et al., (2002): National Growth Charts for Egypt.
12. Herman TE and Siegel MJ. Miller--Dieker syndrome, type 1 lissencephaly J Perinatol. 2008; 28(4):313-5.
13. Poirier K, Keays D, Francis F, et al. Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in Tubulin Alpha 1A (TUBA1A). Hum Mutat. 2007; 28: 1055–64
14. Barkovich J and Raybaud C. Neuroimaging in disorders of cortical development. Neuroimaging Clin N Am 2004;14:231–54, vii
15. Abdel Razek A.A.K., Kandell A.Y., Elsorogy L.G., et al. Disorders of Cortical Formation: MR

Imaging Features. AJNR Am J Neuroradiol 2009; 30:4 –11.
16. Barkovich J, Kuzniecky R, Jackson G, et al. A developmental and genetic classification for malformations of cortical development. Neurology 2005;65:1873–87
17. Rajab A, Chiara M, Ganeshwaran H., Christopher A. Walsh G, and M. Elizabeth Ross5. A Novel form of lethal microcephaly with simplified gyral pattern and brain stem hypoplasia. American Journal of Medical Genetics 2007; Part A 143A:2761–2767.
18. Zanelli SA, Stanley MP and Kaufman DA. Hypoxic Ischemic Encephalopathy. E-medicine, pediatrics, Neonatology. 2009 Available at http://e.medicine.com/ped/topic 149.htm
19. Adcock L., and Papile L. Perinatal asphyxia. In: Manual of Neonatal care. Cloherty J., Eichenwald E. and Stark A. (eds).6th spiral edition. Lippincott Wlliams and Wilkins. USA 2008; 27C:518-528.
20. Hahn J. and OlsonM. Etiology of Neonatal Seizures. NeoReviews 2004; 5(8):327.
21. Valeo, Tom . Mri Study Finds White Matter Damage in Cerebral Palsy; Neurology Today: 7 November 2006 - Volume 6 - Issue 21 - pp 1,9
22. Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology 2003;60:367–380.
23. Harald E. Möller, P, Josef W, Ulrich B, Dirk W, Reinhold F, Kurt U. Brain Imaging and Proton Magnetic Resonance Spectroscopy in Patients with Phenylketonuria. PEDIATRICS Vol. 112 No. 6 December 2003, pp. 1580-1583.
24. Hähnel S. Brain MRI Abnormalities in Phenylketonuria an Update on MR Imaging and MR Volumetry Clinical Neuroradiology 2008:18; No. 1, 19-24.
25. Radmanesh A, Zaman T, Ghanaati H, et al. Methylmalonic acidemia: brain imaging findings in 52 children and a review of the literature. Pediatric Radiology 2008; 38, 1054-61.
26. Girgs M.Y.,Abd El Hady S.and Selim L. et al .White and grey matter abnormalities in some neurometabolic disorders :A clinicoradiological correlation. Alex Pediatr 2008; 22(2):319-327.
27. Kim S, In-One K, Woo S, Yun S, Lee G, Ok K, Kyung M, Ki K, and Yong H: MR of Childhood Metachromatic Leukodystrophy. AJNR Am J Neuroradiol 1997; 18:733–738
28. AL Kartikasalwah, LH Ngu . Leigh syndrome: MRI findings in two children Biomedical Imaging and Intervention J 2010; 6(1):e6
29. Moog U., Smeets E.E., Van Roozendaal K.E., et al .Neurodevelopmental disorders in males related to the gene causing Rett syndrome in females (MECP2). Eur J Paediatr Neurol. 2003;7(1):5-12.
30. Carter J.C., Lanham D.C., Pham D. Selective Cerebral Volume Reduction in Rett Syndrome: A Multiple-Approach MR Imaging Study. AJNR Am J Neuroradiol 2008;29:436–41

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