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Pediatric Mitochondrial Disease: Experience from A Tertiary Care Hospital in Bangladesh

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Abstract

Background: *Mitochondrial diseases are rare group of heterogeneous, genetically determined disorders that affect multiple organs with variable severity due to the dysfunction of mitochondria. They usually present with acute or chronic features with intermittent decompensation. The common features are neuro-regression, hypotonia, failure to thrive, stroke, seizures, myopathy, cardiomyopathy, deafness, blindness, movement disorder, lactic acidosis etc. The aim of this study was to describe the clinical, neuroimaging and genetic analysis of mitochondrial diseases.*

Methodology*: This retrospective study was done among sixteen admitted patients in the Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2016 to December 2023.*

Results: *Total sixteen patients were included in the study. The age of the patients ranged from 3 months-8 years; 11 patients were male. Developmental delay and regression, seizure, hypotonia, dystonia, ataxia were the key clinical manifestations. About 12.5% had persistent hypoglycemia. 6.13% presented with periodic paroxysms of dyskinesia and weakness. In MRI of brain, predominant feature was bilateral basal ganglia involvement. Genetic analysis showed variable presentation. Here, 12.5% was diagnosed with Leigh syndrome, 12.5% had primary carnitine deficiency, 12.5% had SURF-1 mutation causing mitochondrial complex IV deficiency, 6.13% had mitochondrial short chain enoyl co-A hydratase deficiency,12.5% had mitochondrial DNA depletion syndrome and 6.13% had progressive external ophthalmoplegia with mitochondrial DNA deletions.*

Conclusion: *Multisystem heterogenous involvement gives a clue to the suspicion of mitochondrial disease in pediatric population.*

Keyword: *Mitochondrial disease (MD), clinical features, neuroimaging, genetic study.*

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Introduction

Mitochondrial diseases (MD) are a diverse group of disorders that are caused due to defect in the electron transport chain or respiratory chain within the mitochondria[1] MD usually present with clinical, biochemical and genetic complexity[2]. Phenotypes vary from solely myopathy to multi organ involvement with variable age of onset, severity, and progression[1]. Common presentations are acute or chronic features with intermittent decompensation. The common clinical features are neuroregression, hypotonia, failure to thrive, seizures, cardiomyopathy, deafness, blindness, movement disorder, and lactic acidosis[3,4,5].

The first MD was described by Luft in 1959 and mitochondrial genome sequencing was published in 1981 . The first pathogenic mutation in mitochondrial DNA was identified in 1988w. At present, more than 350 genes' pathogenic point mutations, deletions, insertions, and rearrangements in both mitochondrial and nuclear genomes are established to cause primary MDx. This disorder may have maternal, X linked, autosomal recessive, autosomal dominant, and de novo occurrence[8,9]. Common MD are Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), Leber hereditary optic neuropathy (LHON), Leigh syndrome, Kearns-Sayre syndrome (KSS), Myoclonic epilepsy and ragged-red fiber disease (MERRF), mitochondrial DNA depletion syndrome, mitochondrial neurogastrointestinal

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encephalopathy (MNGIE), neuropathy, ataxia, retinitis pigmentosa syndrome (NARP)u .

The true incidence and prevalence of MD is unknown, in some studies it was seen that approximately 1 in 8000 people had pathogenic mutation for mitochondrial diseasev . Very limited study has been published from Bangladesh on this disorder particularly with genetic profile. Thus, this study was done to describe the clinical profile, neuroimaging, genetic profile of various MD in a tertiary care center in Bangladesh.

Materials & Methods

This retrospective study was done in the Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Sixteen admitted children who were diagnosed as MD from January 2016 to July 2023 were included in this study. The diagnosis was done on the basis of clinical features, neuroimaging, electroencephalography, biochemical features and genetic study.

We collected the clinical data of all sixteen patients retrospectively. Detailed history from registrar book regarding the demographic profile, detailed family and birth history, antecedent illness, age of onset, age at presentation, presenting clinical features were taken. Clinical examination including neurological examination findings were also taken from the registrar. Consent from the patients' parents were taken during admission. Basic metabolic screening, cerebrospinal fluid (CSF) study (routine, lactate), Electroencephalogram (EEG), MRI of brain with contrast and MRS were done in patients according to the indication. In selected case Tandem mass spectrometry (TMS) and Gas Chromatography Mass Spectrometry (GCMS) was done. In every patient next generation sequencing including mitochondrial whole genome sequencing was advised. Genetic test was done in 8 patients. Each patient was treated symptomatically and with mitochondrial cocktail.

Results

The age of the patients were ranged from 3 months-8 years. Eleven patients were male out of 16. One patient developed clinical manifestation at 6 and ½ years (Table I). Developmental delay and regression, seizure, hypotonia, dystonia, ataxia were predominant clinical features.About 12.5% had persistent hypoglycemia, 6.13% cases presented with periodic paroxysms of dyskinesia and weakness and one patient presented with cataract (Table II). Most of the cases were precipitated by fever. Bilateral basal ganglia involvement on MRI was found in most of the cases (Table IV) (Fig 1,2,3). Other findings were midbrain hyperintensity and dentate nucleus hyperintensity (Fig 4, 5). Genetic analysis and other investigations showed 12.5% cases had Leigh syndrome, 12.5% had Primary Carnitine Deficiency, 12.5% had Mitochondrial DNA Depletion Syndrome, 6.13%had SURF-1 mutation causing mitochondrial complex IV deficiency, 6.13% had mitochondrial short chain enoyl co-A hydratase deficiency and 6.13% had progressive external ophthalmoplegia with mitochondrial DNA deletions. (Table III, IV).

Table I

Demographic characteristics of the studied subjects (n-16)

Demographic Features		n(%)
Age at onset		1 month- 6.5 years
Age at diagnosis		3 months -8 years
Sex	Male	11 (69)
	Female	5 (31)
Consanguinity	Present	6 (38)
	Absent	10 (62)

Table II

Clinical features of the studied subjects (n 16)

Clinical features		n(%)
Developmental delay		13 (81)
Developmental regression		9(56)
Microcephaly		2(12.5)
Hypotonia		11 (69)
Hypertonia		2(12.5)
Movement disorder	Dystonia	8(50)
	Ataxia	6 (38)
	Tremor	3(19)
Choreiform movement		3(19)
Paroxysms of dyskinesia		1(6)
Seizure	Myoclonic	3(19)
	GTCS*	3(19)
Other features	Nystagmus	6(38)
	Cataract	1(6)
	Polydactyly	1(6)
	Hypertrichosis	1(6)

GTCS –Generalized tonic clonic seizure

Table-III

Biochemical status of the studied patients (n-16)

Biochemical Profile	n(%)
S. Lactate (increased)	9(56)
Hypoglycemia	2(12.5)
Urine ketone body(positive)	1(6)
Increased CPK	4(25)
CSF lactate(increased)	3(19)
Tandem Mass Spectrometry (TMS) Carnitine Deficiency	2 (12.5)

Table IV

Neuroimaging and EEG profile of the studies subjects (n-16)

MRI of Brain	n(%)
Basal ganglia hyperintensity	8(50)
Dentate nuclei hyperintensity	6(38)
Midbrain hyperintensity	5(31)
Cortical atrophy	3(19)
Corpus callosum thinning	2(12.5)
Cortical hyperintensity	1(6)
Normal	6(38)
MRS	
Lactate peak	4(25)
EEG	
Normal	10(62.5)
Epileptiform discharge	
Focal	2(12.5)
Generalized	2(12.5)
Epileptic encephalopathy	2(12.5)

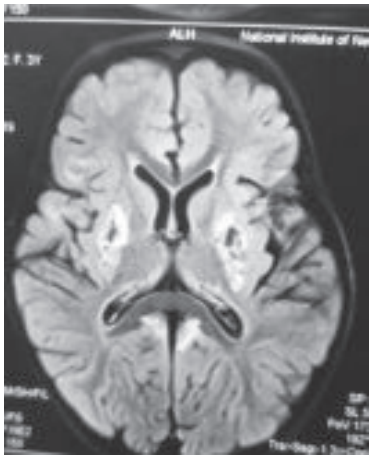

Fig.-1. *MRI of brain FLAIR image showing bilateral basal ganglia mixed intensity*

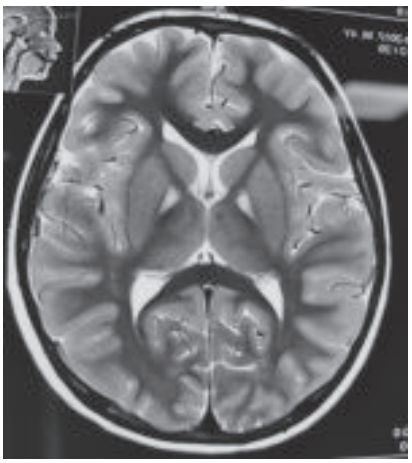

Fig.-2: *MRI of brain T2 image showing bilateral globus pallidus hyperintensity*

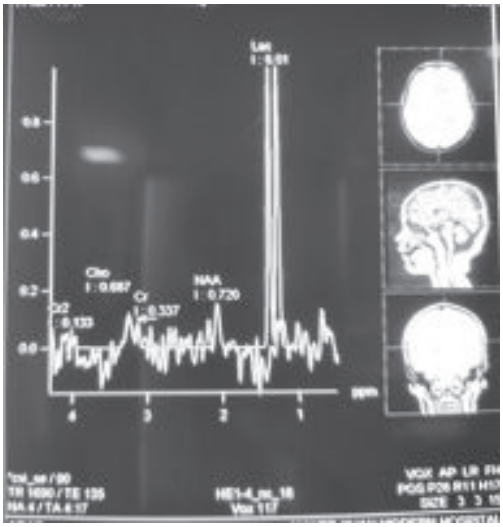

Fig.-3: *MRS showing increased lactate peak*

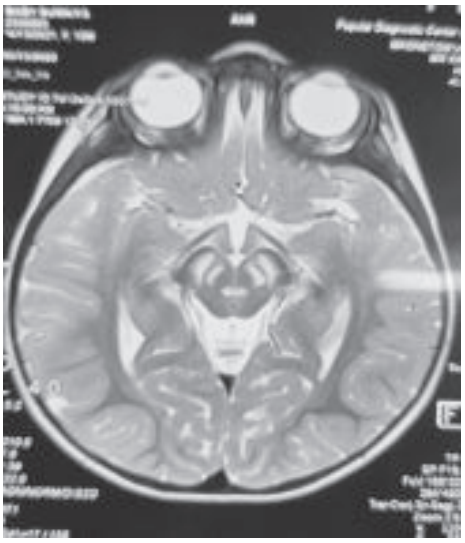

Fig.-4: *MRI of brain showing midbrain hyperintensity*

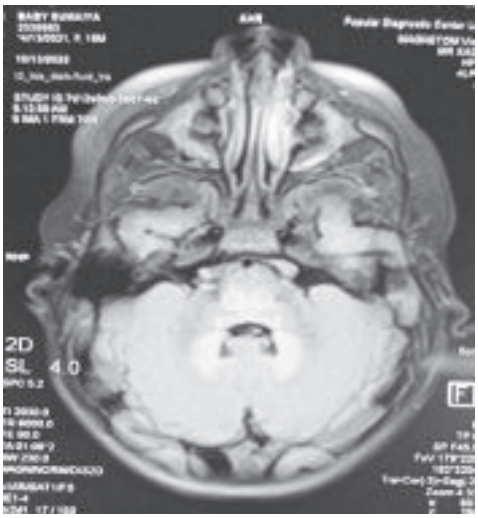

Fig.-5: *MRI of brain showing cerebellar deep nucleus hyperintensity*

Table-V
Genetic profile of the patients (n=16)

Cases	Location	Variance	Gene	Zygocity	Inheritance	Disease	Significance
Case 1 18 month, M	Not done						
Case 2 3 year, M	Exon 1	c.164del, (p. Gly56AlafsTer35)	NDUFAF6(+)	Heterozygous	ARD	Mitochondrial complex 1 deficiency, nuclear type 17	US
Case 3 19 month, F	Not done						
Case 4 2 year, M		c.24A>G(p.Thr9Ala)	MT-ND5+	Homoplasmic	Mitochondrial	Leber hereditary optic atrophy, Leigh syndrome, Mitochondrial Encephalopathy, lactic acidosis, stroke like episodes (MELAS) syndrome	US
		c.1111C>A(p.Leu371Met)	MT-CYB(+)	Homoplasmic	Mitochondrial	Leber hereditary optic atrophy, Leigh syndrome, Mitochondrial Encephalopathy, lactic acidosis, stroke like episodes (MELAS) syndrome	US
Case 5 15 month, M			OPA 1 TARS 2 +ve.	Heterozygous	ARD	Mitochondrial DNA depletion Syndrome	P
Case 6, 3 year, M	Exone 2	c.176A>G(p.Asn59Ser)	ECHS1(-)	Likely compound heterozygous	ARD	mitochondrial short chain enoyl co-A hydratase deficiency	P
	Exone 5	c.518C>T(p.Ala173Val)					LP
Case 7 3 Year, F	Not done						
Case 8 2 year 7 month , F	Not done						
Case 9 6 year, M	Not done						
Case 10 5 year, M	Not done						
Case 11 2 year, F	MT-8701	A>G	MT-APB6		Germline mutation	Leigh syndrome, mitochondrial complex V deficiency	US
Case 12 4 year, M	Not done						
Case 13 2 year F	Exone 8	c.694A>C(p.Thr232Pro)	NDUFv2(+)	Heterozygous	ARD	Mitochondrial complex 1 deficiency, nuclear type 7	US
	Exone 18	c.2891G>A(p.Arg964His)	POLG(-)	Heterozygous	ARD	Mitochondrial DNA depletion syndrome	US
Case 14 8-year, M		c.1301A>G(p.Lys434Arg)	DNA2	Heterozygous	ADD	Progressive external ophthalmoplegia, mitochondrial DNA deletions	US
Case 15 3-year, M	Exone 8	c.792_793del(p. Arg264SerfsTer27)	SURF1(-)	Homozygous	ARD	Mitochondrial complex IV deficiency, nuclear type 1	P
Case 16 18-month, M	Not done						

P, pathogenic; F, LP, likely pathogenic; ARD, autosomal recessive disorder; ADD: Autosomal dominant disorder; US, uncertain significance; M-male, F-Female

Discussion:

MD are heterogenous group of inherited, metabolic disorders with systemic or organ-specific symptoms showing poor phenotype–genotype correlation[10,11]. The mitochondrial respiratory chain is the essential final common pathway for aerobic metabolism; tissues and organs that are highly dependent on aerobic metabolism are preferentially involved in MD[5]. The most frequently involved organs are the muscle, nervous system, endocrine glands, heart, and gastrointestinal tract[9]. Among our study population, two cases were diagnosed as Leigh syndrome, two had primary carnitine deficiency, one had SURF-1 mutation causing mitochondrial complex IV deficiency, one had mitochondrial short chain enoyl co-A hydratase deficiency, two had mitochondrial DNA depletion syndrome and one had progressive external ophthalmoplegia with mitochondrial DNA deletions.

Leigh syndrome (LS) is a classic example of MD resulting from pathogenic mutations that hampers oxidative phosphorylation (OXPHOS) capacities[12]. Patients usually present in infancy and in early childhood. There is delayed milestones or regression of the achieved milestones of development, abnormal muscle tone, weakness, dystonia, brainstem and cerebellar dysfunction, visual loss and seizures. Associated mitochondrial enzyme deficiencies are those of pyruvate carboxylase, pyruvate dehydrogenase, cytochrome C oxidase, and Complex 1[4]. It can be both due to nDNA mutation and mtDNA mutation[12]. Laboratory analysis shows metabolic acidosis with elevated blood, CSF lactate, and pyruvate concentrations. The most characteristic neuro-radiological findings are bilateral , symmetric focal hyperintensities and necrotizing lesions in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei[13,14]. Leigh Disease may also present with some atypical presentation. In a case series, it showed five patients presented with atypical features like progressive flaccid paralysis, progressive diplegia and bronchiolitis like clinical symptoms and normal lactate¹u in our study, two patients were genetically confirmed as Leigh syndrome who presented with loss of developmental delay and regression, hypotonia, dystonia, ataxia. Another six were diagnosed as Leigh syndrome on the basis of clinical features, MRI and MRS findings and biochemical features. Among them seven participants had increased blood lactate, three had increased CSF lactate. MRI showed basal ganglia mixed intensity lesion along with cerebellum, brainstem involvement in six patients. Six of them showed high lactate peak in MRS. Next generation sequencing showed MT-APB6 mutation among one of them.

Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are clinically and genetically heterogeneous group of autosomal recessive disorders that are manifested by a severe reduction in mtDNA content causing disrupted energy production in affected tissues and organs[16]. This is caused by mutations in nuclear genes involved in either nucleotide synthesis (TK2, SUCLA2, SUCLG1, RRM2B, DGUOK, MPV17 and TYMP) or mtDNA replication (POLG, C100rf2). The MDSs can be divided into four types: hepatocerebral, myopathic, encephalomyopathic and neurogastrointestinal¹w . Among our study cases, two were diagnosed as MDS. The clinical features were early onset dystonia, developmental delay, tremor and ataxia. One patient presented with opisthotonic posturing and myoclonic seizure. MRI of brain revealed cortical atrophy in both the patients and one patient had corpus callosum thinning with putamen and thalamus hyperintensity. In one patient EEG revealed epileptic encephalopathy. Genetic study revealed POLG (-) mutation in one patient and the other showed OPA 1 & TARS 2 mutation. (Table 5)

Systemic primary carnitine deficiency is an autosomal recessive disorder that hampers carnitine transportation. They present with episodes of hypoketotic hypoglycemia, hepatomegaly, elevated transaminases, and hyperammonemia; myopathy, elevated creatine kinase (CK), and cardiomyopathy. The diagnosis is confirmed by low plasma free carnitine concentration[3,18,19]. In this study, two brothers, now 6 years and 5 years respectively of 2nd degree consanguineous parents were diagnosed as Primary Carnitine Deficiency. They presented with motor delay, speech delay, cognitive impairment, generalized tonic clonic seizure. Both of them had hepatomegaly, persistent hypoglycemia since early age. MRI of brain and EEG were normal in both the cases. TMS showed low free carnitine (C0), Acetyl Carnitine (C 2), Octadecanoylcartinine (C18) level.

SURF1 deficiency is an autosomal recessive mitochondrial disorder associated with cytochrome c oxidase (COX, complex IV) deficiency. COX is the fourth complex in the mitochondrial oxidative phosphorylation (OXPHOS) system, where complexes I–IV couple sequential electron transfer with proton

pumping[2].SURF1 mutation results in Leigh syndrome and other metabolic disorders [12]. Some of them present with hypertrichosis[201,21]. In our case series, two sibs of non-consanguineous parents presented with ataxia, tremor at 18 months of age following febrile illness. One had hypertrichosis and polydactyly. Both of them showed increased blood lactate. We have investigated thoroughly in one sib who showed normal MRI and genetic study revealed autosomal recessive SURF-1 mutation.

Short Chain Enoyl Co-A Hydratase (*ECHS1*) deficiency is a phenotypically complex disorder. The key features are hypotonia, respiratory insufficiency, global developmental delay, encephalopathy, sensorineural hearing loss, cardiomyopathy, and bilateral basal ganglia lesions. Some patients present with isolated paroxysmal dystonia that may be exacerbated by illness or exertion. T2 hyperintensity in any part of basal ganglia is very common [22]. One case of this study presented with episodic attacks of involuntary movements since 2 years of age precipitated by illness. His MRI showed hyperintensity in globus pallidus. Genetic study revealed *ECHS1* (-) mutation.

Progressive external ophthalmoplegia (PEO) is a common mitochondrial disorder presented with progressive bilateral ptosis and ophthalmoparesis. It may present alone or may be associated with multisystemic disease presentations[3]. In this study, one patient's genetic study revealed DNA2 mutation that was pathogenic for PEO, mitochondrial DNA deletions. He presented with episodic attacks of dyskinesia, irritability, speech difficulty and cataract.

In every patient of the study group, symptomatic management was given in the form of antiseizure medication in seizure, antidystonic drugs, behavioral management, physiotherapy etc. Mitochondrial cocktail was given according to the genotype and phenotype.

Conclusions

Mitochondrial Disease are rare disorders with heterogeneous phenotypes. Probably this is the first case series of MD published from Bangladesh. Here we present sixteen patients of different mitochondrial disorders where neuroregression, movement and tone abnormality and multisystem involvement were the key features.

Recommendations

A further study can be designed in large scale to co relate the clinical findings, neuro imaging and their corresponding next generation sequencing. It will help to diagnose and manage children with MD with greater accuracy.

Limitation

The population size was small and genetic analysis could not be executed in all the study participants.

Conflict of interest:

There was no conflict of interest.

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