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Shedding light on the phenotypic–genotypic correlation of rare treatable and potentially treatable pediatric movement disorders

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Abstract

Background: Advances in genetic science have led to the identification of many rare treatable pediatric movements disorders (MDs). We explored the phenotypic–genotypic spectrum of pediatric patients presenting with MDs. By this, we aimed at raising awareness about such rare disorders, especially in our region. Over the past 3 years, we reviewed the demographic data, clinical profile, molecular genetics and other diagnostic workups of pediatric patients presenting with MDs.

Results: Twelve patients were identified; however, only six patients were genetically confirmed. The phenomenology of MDs ranged from paroxysmal kinesigenic choreoathetosis (1 patient), exercise-induced dyskinesia (2 patients), ataxia (2 patients) and dystonia (2 patients). Whole-exome sequencing in addition to the functional studies for some patients revealed a specific genetic diagnosis being responsible for their MDs. The genetic diagnosis of our patients included infantile convulsions and paroxysmal choreoathetosis syndrome and episodic ataxia due to "pathogenic homozygous mutation of *PRRT2* gene," glucose transporter type 1 deficiency-exercise induced dyskinesia due to "De Novo pathogenic heterozygous missense mutation of exon 4 of *SLC2A1* gene," aromatic L amino acid decarboxylase deficiency due to "pathogenic homozygous mutation of the *DDC* gene," myopathy with extrapyramidal signs due to "likely pathogenic homozygous mutations of the *MICU1* gene," mitochondrial trifunctional protein deficiency due to "homozygous variant of uncertain significance (VUS) of *HADHB* gene" and glutaric aciduria II with serine deficiency due to "homozygous VUS for both *ETFDH* and *PHGDH* genes." After receiving the treatment as per recognized treatment protocols, two patients showed complete resolution of symptoms and the rest showed variable responses.

Conclusion: Identifying the genetic etiology of our patients guided us to provide either disease-specific treatment or redirected our management plan. Hence, highlighting the value of molecular genetic analysis to avoid the diagnostic odyssey and identify treatable MDs.

Keywords: Ataxia, Dyskinesia, Dystonia, Genotype, Movement disorders, Phenotype, Whole-exome sequencing

Introduction

Pediatric movement disorders (MDs) are a large group of heterogeneous neurological disorders presenting during childhood until adolescence [1]. Several factors sometimes render the diagnosis quite challenging in this age group. Some of these factors are related to overlapping or variable phenotypes even within the same family.

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Phenotypic variability is mainly due to variable penetrance and/or variable expressivity of the same mutation [2]. Other factors could be related to age-related variability in the phenotypic presentation [1], lack of expertise [3], rarity of some disorders [4] and limited resources for diagnostic genetic analysis in our region [5].

Generally, there are three groups of MDs identified: hyperkinetic and hypokinetic MDs and ataxia. Hyperkinetic MDs also called "dyskinesias" such as dystonia, chorea and myoclonus are prevailing among the pediatric age group, whereas hypokinetic disorders such as Parkinson's disease are prevailing in adults [6]. Ataxia is neither a hyper- nor a hypokinetic MDs rather it is the inability to perform a well-coordinated voluntary movement that cannot be explained by muscle weakness or involuntary movements [7]. Noteworthy to mention is that pediatric MDs can also be paroxysmal due to episodes of neurological dysfunction that are either isolated or part of a more complex disorder. Paroxysmal MDs include both paroxysmal dyskinesia, consisting of attacks of dystonic and/or choreic movements, and episodic ataxia (EA), characterized by attacks of cerebellar ataxia [8].

Owing to the revolution in genetic science in the past two decades, various genetic etiologies of inherited MDs have been identified resulting in better understanding of genotype–phenotype correlations. This has led to better knowledge about specific treatments, dietary modifications, avoidance of certain triggers and enzyme replacement therapy [4]. This implies an urgent need for early recognition of the underlying etiology aimed at modifying the disease course rather than providing symptomatic treatment.

In this study, we will review and analyze the clinical and genetic profile as well as the treatment response among pediatric patients diagnosed at our clinic with rare genetic treatable and potentially treatable MDs. By this, we aim to offer a better understanding among pediatricians and child neurologists of phenotypic variability to ensure early diagnosis and avoid the diagnostic odyssey with other neurological disorders.

Methods

Ethical approval and patient screening

The ethical approval for this study was granted by the Institutional Review Board at the American Center for Psychiatry and Neurology in Abu Dhabi, UAE. All activities were carried out with ICH GCP compliance. The patients were screened during the period of February 2018 to February 2021. Pediatric patients presenting with possible MDs, exercise intolerance, muscle pain/cramps or abnormal gait were evaluated by taking a detailed history and undergoing a thorough neurological examination. Once patients were identified as having possible MD, the caregivers were counseled about the possible genetic diagnosis and the required genetic test.

An informed consent form was signed by the patients' caregivers. Blood samples for whole-exome sequencing (WES) were collected using the CentoCard (Centogene AG, Germany) following the standard protocol.

Clinical investigation

The demographic data including gender, age at "onset of symptoms, presentation and last visit," ethnicity, mode of delivery, parental consanguinity, perinatal and family history were reviewed for all the patients who were identified with pathogenic, likely pathogenic or variant of uncertain significance (VUS) in the WES analysis. We analyzed the phenotypic presentation of the MD in terms of onset, duration, frequency, triggering factors, associated symptoms and signs. Other comorbidities such as "recurrent chest infections, speech delay, feeding and intellectual difficulties" and effects on ambulation were described. In the diagnostic workup biochemical studies, electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) findings were included.

Biochemical analysis and WES

Double-stranded DNA capture baits against approximately 36.5 Mb of the human coding exome (targeting > 98% of the coding reference sequence and Gencode v28 regions, which was obtained from the human genome build GRCh37/hg19 on May 2018) were used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit. The generated library was sequenced on an Illumina platform to obtain at least 20 × coverage depth for > 98% of the targeted bases. The bioinformatics pipeline included read alignment to GRCh37/hg19 genome assembly, variant calling and annotation, and comprehensive variant filtering. All disease-causing variants reported in HGMD®, in ClinVar and in CentoMD® as well as all variants with minor allele frequency (MAF) below 1% in the gnomAD database are considered. The investigation for relevant variants is focused on coding exons and flanking ± 20 intronic bases.

Additional tests

Additional functional tests were performed for three of our patients whose WES showed VUS to determine the likelihood of the pathogenic or benign nature of their variants. This was applied in the following patients:

- Patient 3, the functional enzymatic activity of L-amino decarboxylase enzyme.
- Patient 4, functional studies included western blot on cultured fibroblast for a MICU1 protein prod-

uct. Moreover, measurement of the respiratory chain enzymes, Complex V and the reference enzymes citrate synthetase was done for functional analysis of NDUFAF6 gene activity.

- Patient 6, measurement of cerebrospinal fluid (CSF) and blood serine level and in silico analysis of glutaric acid protein for functional study of products of both PHGDH and *ETFDH* genes, respectively.

The received diagnosis and treatment before presentation were described. Finally, the treatment received after confirming the genetic diagnosis and its effect on clinical outcome was highlighted.

Results

Twelve patients were identified to have possible MDs during the study period. Blood samples for WES were collected from six patients. One male patient was treated based on the genetic diagnosis of his elder brother with complete resolution of symptoms (patient 1). The rest of our patients could not proceed with WES for personal reasons.

All our six patients who were enrolled in the study were born via spontaneous vaginal delivery (SVD) with an uneventful perinatal course and good Apgar score except for patient 3. All patients were from the Middle East. All parents were 1st degree cousins except patient 2. Detailed patient demographic data and comorbidities are listed in Table 1. The phenomenology of MDs ranged from paroxysmal kinesigenic choreoathetosis (PKC) (1 patient), exercise-induced dyskinesia (2 patients), ataxia (2 patients) and dystonia (2 patients). Two patients presented with seizures (patient 1 and 6). Further phenomenology details, triggering factors, clinical features and course are described in Table 2.

Clinical presentation and the diagnostic work

Patient 1: A 5-year-old boy who presented with 3 different types of events- seizures during infancy, EA at the age of 1 year and PKC a combination of "dystonic/choreoathetotic" movements at the age of 3 years. The genetic diagnosis of infantile convulsions and paroxysmal choreoathetosis (ICCA) syndrome and EA were confirmed based on WES analysis which revealed a pathogenic homozygous mutation of *PRRT2* gene (c.880-34G>A: p.(?)). His younger brother had PKC at the age of 14 months; however, parents did not want to proceed with further genetic testing. Both siblings were prescribed a low dose of carbamazepine with complete resolution of symptoms. The elder brother had learning difficulties. Otherwise, both parents and the elder sister were asymptomatic.

Patient 2: A 9-year-old girl who presented with recurring events of weakness and inability to walk. They were initially infrequent (once/a few times per month) but later became more frequent (once per week) after swimming classes. Reportedly, at the age of 3 and 9 months, she had paroxysmal eye movements that lasted for a few seconds and subsided on their own. Her WES analysis showed De Novo pathogenic heterozygous missense mutation of exon 4 of *SLC2A1* gene (c.457c>T; pArg-153Cys) confirming the diagnosis of glucose transporter type 1 (GLUT-1) deficiency-exercise induced dyskinesia. Her symptoms were resolved by a modified Atkins diet but she will become symptomatic whenever she is off ketosis.

Table 1 Patient's demographic data and comorbidities

Patient	Gender	Age at onset (years)	Age at diagnosis (years)	Current age (years)	Parental consanguinity	Family history	Comorbidities
P1	Male	0.83	5	7.8	1st cousins	Younger brother has PKC Elder brother has learning difficulties	Speech delay
P2	Female	2	9	12	No	No	Learning difficulties
P3	Male	Since birth	1.5	4.5	1st cousins	No	Recurrent chest infections Feeding difficulties Failure to thrive
P4	Male	5	13	17.7	1st cousins	Elder brother and maternal aunt had spasticity and ichthyosis	Speech difficulties Failure to thrive
P5	Male	6	16	20	1st cousins	Mother's sister had facial twitching movements	Dysphagia and recurrent chest infections during childhood
P6[a]	Female	2.1	4	6	1st cousins	Maternal grandmother had hypoglycemia	Strabismus Failure to thrive

[a] Published in Ali A. et al. Genes[10]

Table 2 Patient's phenomenology, clinical features and course

Patient	Phenomenology	Onset	Duration	Frequency of events	Triggers	Associated symptoms	Associated signs	Ambulation/ Course
P1	1-BFIC 2-PKC 3-EA	Acute Episodic Episodic	3–5 min 1–2 min 10–15 days	2–3/week 5–8/day 1–2/year	No Physical exertion No	Slurred speech	Sneezing/yawning following the event Intention tremors	Ambulatory/static
P2	Exercise induced dyskinesia	Episodic	30 min	Once/week	Exercise Fasting Febrile illness	Poor balance and fine motor skills	Paroxysmal eye movements Appendicular hypotonia Intension tremors	Ambulatory/static
P3	Dystonia (facial and whole body)	Episodic	1–4 h	4–8/day	Diurnal variation Lack of sleep Febrile illness	Sleep disturbance Agitation Nasal congestion Constipation Excessive sweating and salivary secretions	Autonomic instability with hypotension Oculogyric crises Bilateral ptosis Truncal hypotonia Appendicular hypertonia	Non-ambulatory/ progressive
P4	Dystonia	Mixed	10–15 min	3–6/day	Emotional excitement or fear	Skin dryness Weakness Frequent falling Abnormal gait	Eczema Proximal muscle weakness Brisk reflexes in the lower extremities Spasticity in lower extremities Bilateral feet deformity	Ambulatory with difficulties/progressive
P5	Exercise induced dyskinesia, muscle cramps and pain	Episodic	Hours-days	1–2/week	Exercise	Droopy eye lids and 2^{ry} inability to walk during childhood Left sided facial and neck twitching	Proximal weakness in the lower extremities Positive Gower sign following exercise Brisk reflexes in the upper extremities Absent ankle reflexes	Ambulatory/static
P6[a]	1-Ataxia 2-Refractory seizures 3-Psychomotor regression	Acute	Throughout the day	Daily	Febrile illness Valproic acid	Feeding difficulties and constipation during infancy Psychomotor regression Poor fine motor skills	Microcephaly Slurred speech Mild generalized hypotonia Proximal muscle weakness	Walk but cannot run or jump/static

BFIC benign familial convulsions, *EA* episodic ataxia, *PKC* paroxysmal kinesigenic choreoathetosis

[a] Published in Ali A. et al. Genes[10]

Patient 3: An 18-month old boy who was initially diagnosed with cerebral palsy and epilepsy secondary to hypoxic-ischemic brain injury. He was born at 39 weeks, SVD, Apgar score was 5, 7 and 8 at 1, 5 and 10 min, respectively. He was admitted to the NICU for 2 weeks due to respiratory difficulties and hypotension (mean BP 40–45 mmHg). He was noted to have less eye-opening and normal neurological examination. Soon after discharge, he had recurrent daily events of facial dystonia and whole body dystonic posturing. His WES analysis showed pathogenic homozygous mutation of the *DDC* gene (c.242C>T; p.Pro81Leu). Additional functional

measurement of aromatic L-amino acid decarboxylase (AADC) activity in the plasma showed low enzymatic activity which confirmed the diagnosis of Aromatic L-amino acid decarboxylase (AADC) deficiency according to the consensus guidelines diagnostic recommendations [9], as shown in Tables 3 and 4. His autonomic symptoms, disturbed sleep pattern, agitation and dystonic crisis showed remarkable improvement after receiving treatment but he was still profoundly delayed as shown in Table 5.

Patient 4: A 13-year-old boy who was previously healthy except for a history of febrile seizures during infancy. He presented with walking difficulties at the age of 5 years. He was diagnosed with possible hereditary spastic paraplegia. At the age of 12 years, he developed sudden dystonic posturing with loss of balance and falling triggered by emotional excitement. His elder brother had severe spasticity and ichthyosis for which he was investigated for possible Söjgren Larsson syndrome, but the results were normal.

His WES analysis detected likely pathogenic homozygous mutations of the *MICU1* gene (c.553C>T; p.Gin185) and a VUS of NDUFAF6 genes (c.808C>G; p.Leu270Val). The result of WES was matched with a diagnosis of myopathy with extrapyramidal signs (MPXPS) caused by a variant detected in the *MICU1* gene. However, to rule out a contribution of *NDUFAF6* variant to the phenotype of the patient, additional respiratory chain functional evaluation and western blot assessment were performed for *NDUFAF6* and *MICU1* gene products, respectively, in cultured fibroblasts. Activities of respiratory chain enzymes, Complex V and the reference enzymes citrate synthetase in cultured fibroblasts showed normal activities. These results made it unlikely that the *NDUFAF6* variant that has been identified in our patient to be pathogenic. On the other hand, western blot experiments on fibroblast of the patient to assess the expression levels of the MICU1 protein showed that there was reduced expression of the protein in the patient cells, in comparison with the levels in control cells.

Patient 5: A 16-year-old boy who had an acute generalized weakness with bulbar dysfunction following a febrile illness at the age of 6 years. He was suspected to have Guillain–Barre syndrome versus myasthenia gravis. He was given intravenous immunoglobulins and was finally treated as a case of immune-mediated myasthenic syndrome. His symptoms including weakness even without exertion, walking difficulties, dysphagia and recurrent chest infections persisted even while receiving pyridostigmine. So, treatment was discontinued. Later on, his symptoms were limited to exercise-induced muscle weakness, cramps and pain. He was investigated at our clinic at the age of 15 years and was genetically confirmed to have mitochondrial trifunctional protein deficiency (MTP) caused by homozygous VUS of *HADHB* gene (c.397A>G; p.Thr133Ala).

Patient 6: A 3-year-old girl who had a positive neonatal screening for glutaric aciduria II (GA-II) and non-conclusive acylcarnitine test. She did not have any clinical concerns until she had her 1st unprovoked seizure at the age of 25 months with subsequent psychomotor regression. She was also noted to have an unsteady gait with frequent falling and speech difficulties. She was maintained on valproic acid, lamotrigine and clonazepam. She failed to respond to two other antiepileptic drugs (AEDs). At the age of 3 years, she presented at our clinic for a second opinion. Her seizure was described as behavioral arrest, staring with eyelid flutter. The mother reported that valproic acid showed the best seizure control. However, it worsened her gait and balance. At this point, EEG showed very frequent multifocal epileptiform discharges arising independently from either posterior temporo-occipital head region, more on the right side as shown in Fig. 1a, b. The molecular studies for neuronal ceroid lipofuscinosis were requested; however, she was referred to complete her neurometabolic work up at the tertiary hospital metabolic clinic. Her WES analysis revealed homozygous VUS for both *ETFDH* and *PHGDH* genes. The patient was confirmed to have GA-II with serine deficiency using biochemical studies and in silico analysis as shown in details in Tables 3 and 4. The patient's detailed neurometabolic/genetic workup was also published by my colleagues [10], since we shared her clinical care. However, we were keen to share our experience with this joint patient as part of our treatable/potentially treatable MD case series. After receiving the proper treatment protocol and weaning off valproic acid, her seizures were well controlled as shown in Table 5.

The detailed diagnostic workup carried out during the patient's journey from the beginning of symptoms till reaching the confirmed genetic diagnosis is displayed in Tables 3 and 4.

After reaching the proper genetic diagnosis of our patients, they were maintained on the universally recognized treatment protocol for such diagnosis. Two patients showed complete resolution of symptoms, one patient showed remarkable improvement and 3 patients showed some symptomatic relief as shown in Table 5.

Discussion

Here in this study, we analyzed the detailed phenotypic–genotypic relationship in six patients presenting with MDs at our pediatric neurology division. All patients were Arabs. All parents were 1st degree cousins except one, emphasizing the impact of consanguineous marriage on the increased rate of autosomal recessive

Table 3 Patient's diagnostic work up, previously received diagnosis and treatment

Patient	Brain MRI	EEG	Serum	Urine	CSF	Other studies	Diagnosis prior to presentation	Treatment prior to presentation
P1	Normal	Normal	Normal plasma amino acids, lactate, ammonia, immunological markers, catecholamine levels	Normal urine organic acids	Normal CSF/blood glucose ratio	None	Epilepsy	Valproic acid Lamotrigine Levetiracetam
P2	Normal	Normal	Normal potassium level during the event, CPK, plasma amino acids, acyl carnitine profile, thyroid functions, vitamin B12 and E	Normal urine organic acids and chromatography for uroporphyrins	Low CSF/blood glucose ratio	Molecular investigation for Friedriech ataxia and serum anti-NMDA receptor were negative Pelvi-abdominal ultrasound showed accessory spleen	None	None
P3	Normal	Normal	Normal plasma amino acids, ammonia, lactate, CPK, acyl carnitine profile, total homocysteine level	Normal urine organic acids	None	Aromatic L-amino acid decarboxylase enzymology in plasma: Low dopamine level: 2.50 pmol/min/mL (36.00–129.00 pmol/min/mL)	Cerebral palsy and epilepsy	Valproic acid Baclofen Clonazepam
P4	Normal	None	CPK elevated 1067 IU/L (49–397 IU/L)	None	None	Western blot experiments on fibroblast showed reduced MICU 1 protein	Hereditary spastic paraplegia	Baclofen
P5	Normal	None	Normal CPK, potassium level during the event, thyroid profile, vitamin B12	None	Negative CSF for HSV and EB virus	At the age of 6 years, RNS showed decrement consistent with myasthenia gravis At the age of of 15 years, NCS/EMG showed remote neurogenic process in proximal upper and lower extremities with no evidence of neuromuscular junction or myopathic disorder ECHO mildy dilated left ventricle	Myasthenic syndrome	IVIG Pyridostigmine

Table 3 (continued)

Patient	Brain MRI	EEG	Serum	Urine	CSF	Other studies	Diagnosis prior to presentation	Treatment prior to presentation
P6[a]	Cerebellar atrophy	Multifocal epileptiform discharges	Positive newborn screening for Glutaric aciduria-II Plasma amino acid: severe serine deficiency (42 µmol/L) and mildly reduced glycine (96 µmol/L)	Normal urine organic acid (not performed during the acute episode)	CSF amino acid showed a severe serine deficiency (6 µmol/L), normal glycine (8 µmol/L) Low serine CSF/plasma ratio: 0.14 (Ref > 0.2)	Fibroblast culture from skin biopsy: normal fatty acid oxidation probe assay VEP/ERG mild dysfunction in the optic nerve pathways in both eyes Bilateral optic atrophy ABR normal	Possible neuronal ceroid lipofisciosis	Levetiracetam, oxcarbamazepine Clonazepam Lamotrigine valproic acid

[a] Published in Ali A. et al. Genes[10]

Table 4 Patient's final diagnosis and phenotypic/genotypic correlation

Patient	Phenomenology	Diagnosis	Gene	Zygosity (variant type)	NM number	Nucleotide and protein changes	Type of variant change and its class	In silico prediction	MAF
P1	1-BFIC 2-PKC 3-EA	ICCA	*PRRT2*	Homozygous	NM_001256442.1	c.880-34G>A; p.(?)	Substitution Pathogenic (class I)	PolyPhen-2: N/A Align-GVGD: N/A SIFT: N/A Mutation-Taster: N/A LRT: N/A Conservation: Conserved across mammals	gnomAD: N/R ESP: N/R 1000 G: N/R
P2	Exercise induced dyskinesia	GLUT-1 deficiency	*SLC2A1*	Heterozygous	NM_006516	c.457C>T; p.Arg153Cys	Missense Pathogenic (class I)	PolyPhen-2: Probably damaging SIFT: Damaging Mutation-Taster: Disease causing LRT: Deleterious REVEL: pathogenic PROVEAN: Damaging Conservation: Conserved across species	gnomAD: N/R ESP: N/R 1000 G: N/R
P3	Dystonia (facial and whole body)	AADCD	*DDC*	Homozygous		c.242C>T; p.Pro81Leu	Missense Pathogenic (class I)	PolyPhen-2: Possibly damaging SIFT: Damaging Mutation-Taster: Disease causing LRT: Deleterious REVEL: pathogenic PROVEAN: Damaging Conservation: Conserved across species	gnomAD: N/R ESP: N/R 1000 G: N/R

Table 4 (continued)

Patient	Phenomenology	Diagnosis	Gene	Zygosity (variant type)	NM number	Nucleotide and protein changes	Type of variant change and its class	In silico prediction	MAF
P4	Dystonia	MPXPS	*MICU 1*	Homozygous	NM_006077.3	c.553C>T; p.Gln185*	Nonsense likely pathogenic (class II)	MutationTaster: Disease causing LRT: Deleterious Conservation: Conserved across species	gnomAD: 0.00002 0.002% (4/204610 alleles) ESP: N/R 1000 G: N/R
P5	Exercise induced dyskinesia, muscle cramps and pain	MTP	*HADHB*	Homozygous	NM_000183.2	c.397A>G; p.Thr133Ala	Missense VUS (class III)	PolyPhen-2: Possibly damaging SIFT: Damaging MutationTaster: Disease causing LRT: Deleterious REVEL: pathogenic PROVEAN: Damaging Conservation: Conserved across species	gnomAD: 0.0001061 0.011% (30/282798 alleles) ESP: 0.0116% 1000 G: N/R

Table 4 (continued)

Patient	Phenomenology	Diagnosis	Gene	Zygosity (variant type)	NM number	Nucleotide and protein changes	Type of variant change and its class	In silico prediction	MAF
P6[a]	Ataxia Refractory seizures Psychomotor regression	GA-II Serine deficiency	*ETFDH* *PHGDH*	Homozygous Homozygous	NM_004453.2 NM_00662303	c.679C>A; p.Pro227Thr c.1219T>C; p.Ser407Pro	Missense VUS (class III) Missense VUS (class III)	PolyPhen-2: Probably damaging SIFT: Damaging Mutation-Taster: Disease causing LRT: Deleterious REVEL: pathogenic PROVEAN: Damaging Conservation: Conserved across species PolyPhen-2: Possible damaging SIFT: Damaging Mutation-Taster: Polymorphism LRT: Tolerated PROVEAN: Neutral Conservation: Conserved across mammals	gnomAD: 0.00001193 0.0012% (3/251428 alleles) ESP: 0.0116% 1000 G: N/R gnomAD: N/R ESP: N/R 1000 G: N/R

AADCD, Aromatic L amino acid decarboxylase deficiency; BFIC, benign familial convulsions; EA, episodic ataxia; GA-II, glutaric aciduria type II; GLUT-1, glucose transporter type 1 deficiency; ICCA, infantile convulsions and paroxysmal choreoathetosis syndrome; MAF, minor allele frequency; MPXPS, myopathy with extrapyramidal signs; MTP, mitochondrial trifunctional protein deficiency; N/R, Not Reported; PKC, paroxysmal kinesigenic choreoathetosis; VUS, variant of uncertain significance

[a] Published in Ali A. et al. Genes[10]

genetic disorders in our region [11]. All our patients had triggers that either initiated or had worsened their MDs. Two patients had shown some clinical clues that had raised our clinical suspicion for specific MDs such as "paroxysmal eye movements" in patient 2 and "oculogyric crises and hypotonia" in patient 3. Five patients were initially misdiagnosed and three patients were prescribed inappropriate medications.

Patient 1 was diagnosed with ICCA and EA due to a novel homozygous *PRRT2* pathogenic variant. PRRT2 encodes a protein that is expressed in the central nervous system (CNS) and is thought to be involved in the modulation of synaptic neurotransmitter release. *PRRT2* mutations are associated with a variety of paroxysmal disorders including paroxysmal kinesigenic dyskinesia (PKD), exercise-induced dyskinesia, paroxysmal non-kinesigenic dyskinesia (PNKD) [12], benign familial infantile epilepsy (BFIE), ICCA [13], EA, hemiplegic migraine, intellectual disability and benign paroxysmal torticollis of infancy [14].

ICCA syndrome is a rare neuro-genetic disorder characterized by the association of benign infantile seizures (BIS) during early infancy followed by PKC later in life [13]. EAs are identified by recurrent attacks of cerebellar ataxia lasting for a few seconds up to several days. The most commonly reported causative mutations were detected in the KCNA1 (EA1) and CACNA1A

Table 5 Treatment, response and outcome after confirmed genetic diagnosis:

Patient	Treatment	Response	Outcome
P1	Carbamazepine	Events stopped	Improved speech difficulties
P2	Modified atkins diet	Events stopped	Improved attention span and mood
P3	Trihexyphenidyl (anticholinergic) Bromocriptine (dopamine agonist) Pyridoxine	Symptomatic relief	Less frequent dystonic crises Occasional oculogyric crises Improved sleep and less agitation Improved truncal tone Profound developmental delay
P4	Baclofen Coenzyme Q10 Levocarnitine Low-fat and high carbohydrate diet	Symptomatic relief	Improved spasticity
P5	Diet (medium chain triglycerides during periods of increased activity) Levocarnitine	Symptomatic relief	Less pain and muscle cramps
P6[a]	Lamotrigine and clonazepam Valproic acid (weaned off) L-serine, 1500 mg TID Riboflavin, 100 mg TID Coenzyme Q10, 10 mg OD Levocarnitine, 1000 mg BID Low-fat and high carbohydrate diet	Controlled seizures	Improved ataxia Less frequent falls Mild truncal hypotonia

[a] Published in Ali A. et al. Genes[10]

(EA2) genes [8]. Other rare mutations were detected in SCN2A [15], FGF14 [16] and *PRRT2* genes [14].

PRRT2 mutations are autosomal dominantly inherited. However, some patients with compound heterozygous and others with homozygous mutations were reported [12, 13]. These patients inherit mutation(s) from both asymptomatic parents, which suggests autosomal recessive (AR) inheritance. In addition, incomplete low penetrance of *PRRT2* mutations was reported [13], as evidenced by variable intra-familial expressivity [17]. A similar observation was noted among our patient family members, where both parents and elder sister were asymptomatic, the younger brother had PKC and the elder brother had learning difficulties. It would have been helpful if a genetic analysis was performed to explore variable phenotypic presentation among family members. This warrants particular attention by genetic counselors during counseling families of an affected member.

Genetic analysis of our patient has shown homozygote biallelic splice mutation (c.880-34G>A: p.(?)) leading to an AR inheritance. Similar splicing mutation (c.880-35G>A) of intron 2 was reported in an 18-month-old child presenting with IC, followed by PKD, the mother of whom had PKD only despite having an identical mutation [18]. To our knowledge, our patient is the first to present with both ICCA and EA due to *PRRT2* mutation. This additional finding of EA tends to be present in the case of biallelic mutations as reported by Delcourt et al. [19].

Since early infancy, our patient was misdiagnosed and received multiple trials of AEDs. Similar to previous publications [17, 18], our patient and his brother showed complete resolution of symptoms after receiving low dose carbamazepine, highlighting the importance of revising the diagnosis in cases with idiopathic refractory epilepsy.

Patient 2 was diagnosed with GLUT-1 deficiency-exercise induced dyskinesia based on the genetic analysis showing de novo heterozygous missense mutation of exon 4 of *SLC2A1* gene (c.457c>T; pArg153Cys) and low glucose level in CSF. Most detected *SLC2A1* mutations are "de novo" as in our case. In familial cases, inheritance is autosomal dominant mainly with complete penetrance [20]; however, AR inheritance has been less frequently reported [21, 22].

Glucose is the main source of energy for brain metabolism. Glucose transport protein type 1 (GLUT1) facilitates glucose transport across the blood–brain barrier [23]. GLUT1 deficiency syndrome is due to heterozygous mutations in the *SLC2A1* gene resulting in failure of delivery of glucose into the brain cells [24]. The amount of reduction of GLUT1 protein will affect the severity of the disease phenotype through the haploinsufficiency mechanism. The higher the amount of the protein produced, the milder the clinical phenotype [22]. The phenotypic spectrum includes developmental delay, seizures, acquired microcephaly and various paroxysmal MDs such as ataxia, dystonia and exercise-induced dyskinesia [20, 24]. Our patient had transient

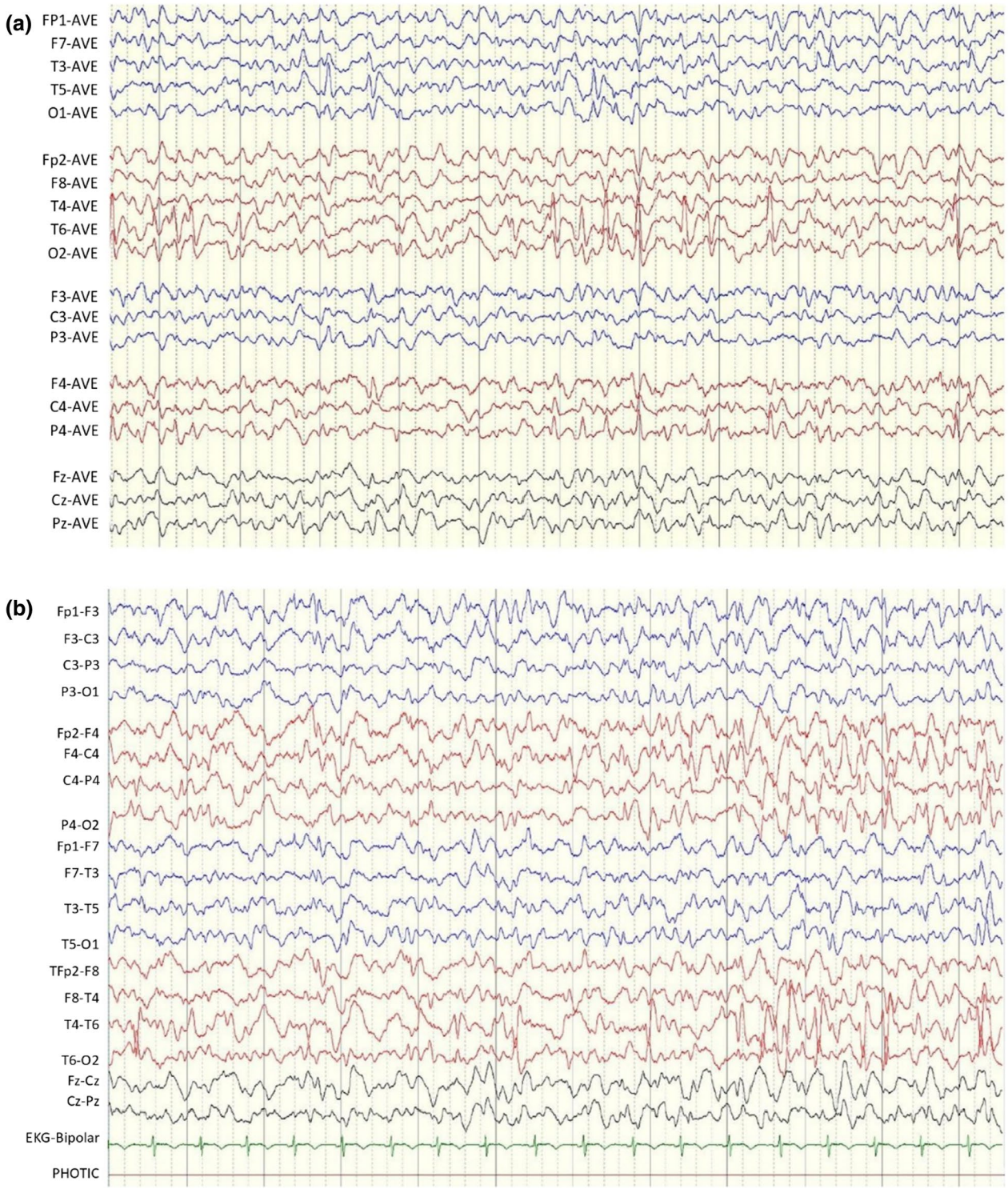

Fig. 1 Two EEG epochs for patient 6, showing multifocal epileptiform discharges. **a** Average montage, **b** bipolar montage

self-limiting paroxysmal eye movements during infancy which is considered one of the earliest clinical features in some patients with GLUT1 deficiency [25]. Later on, she developed exercise-induced dyskinesia during childhood. Our patient responded well to the modified Atkins diet, similar to other studies [24, 26], showing favorable

response especially with early diagnosis and initiation of the dietary therapy.

Patient 3 was diagnosed with AADCD due to a pathogenic homozygous mutation of the *DDC* gene and low AADC enzyme activity in the plasma. Dopamine and serotonin represent the two major monoamine neurotransmitters of the mammalian nervous system [27]. Dopamine is the precursor of norepinephrine and epinephrine [28]. AADC enzyme is the last enzyme involved in the biosynthesis pathway of monoamine neurotransmitters. Therefore, AADC enzyme deficiency will result in severe combined deficiency of serotonin, dopamine, norepinephrine and epinephrine leading to a rare AR neurometabolic disorder known as AADCD [29].

AADCD symptoms typically present during the first months of life. The most important characteristic clinical features of AADCD are hypotonia and oculogyric crises. Most patients have severe phenotypic spectrum in the form of early-onset ptosis, hypokinesia, dystonia, impaired development, failure to thrive and autonomic dysfunction [29]. Milder disease course has been described in a few patients [30].

AADCD is caused by mutations in the *AADC* gene leading to the loss of function of DDC. More than 50 different mutations of the *AADC* gene have been reported, most of them are substitution mutations. However, deletions, insertions and splice mutations also exist [31]. There are no clear genotype–phenotype correlations except for founder splice mutation(s) of the Far East which are associated with the severe phenotype [32]. On the other hand, most substitution mutations result in abnormal protein configuration inducing a remarkable change of loop 1, 2 or 3 of the enzymes which prevent the acquisition of a fully active form of the enzyme [33]. This is the case of the mutation reported in our patient c.242C>T p.(Pro81Leu) which affects loop 1 of the enzyme (residue 66–84). Core diagnostic keys for AADCD rely on three elements: AADC activity in plasma, typical CSF AADCD pattern and detection of homozygous or compound heterozygous mutations. The presence of two positive elements as in our patient is considered to be diagnostic [9].

Unified evidence-based treatment guidelines are lacking, and treatment protocols vary from one center to another due to the rarity of the condition [27]. Based on the available literature, a consensus guideline for the diagnosis and treatment was proposed in 2017, showing variable outcomes with the use of selective dopamine agonists, monoamine oxidase (MAO) inhibitors, pyridoxine and anticholinergic agents [9]. On receiving treatment, our patient showed partial improvement in severity and frequency of dystonia with fewer crises. Therefore, early diagnosis of this rare neurometabolic disease is essential to provide a better outcome and avoid misdiagnosis requiring unnecessary lifelong treatments such as the use of AEDs. Moreover, an emerging gene therapy through bilateral intraputaminal infusions of adeno-associated virus vector harboring DDC has shown some improvement of motor and cognitive abilities. However, more studies are still required for ensuring safety and efficacy in the long term [34, 35].

Patient 4 was diagnosed with myopathy with extrapyramidal signs (MPXPS) due to homozygous likely pathogenic mutation in the *MICU1* gene and reduced expression of MICU1 protein in the fibroblast cells.

Mitochondrial Ca2 + homeostasis is essential for many physiological functions in the neuromuscular system [36]. Physiological Ca2 + level in the mitochondria is required for regulating the aerobic metabolism; on the other hand, Ca2 + overload triggers cell death [37]. Loss of function of *MICU1* gene results in defective mitochondrial Ca2 + signaling, mitochondrial fragmentation [36] resulting in brain and muscle disorder [37]. This has been described as MPXPS which is a rare AR mitochondrial disorder due to mutation in the *MICU1* gene located on chromosome 10q22.1 [38]. MICU1 protein can be detected in cultured fibroblasts by the western blot technique. The absence of expression of this protein in cultured fibroblasts is an indicator of its functional loss [39]. This was demonstrated in our case by western blot analysis of MICU1 protein on cultured fibroblasts.

MPXPS has variable neuromuscular manifestations including muscle weakness, extrapyramidal motor disorders, developmental delay, impaired cognition, hypertrophied calf muscles, hyperkalemia and cardiomegaly [37, 38, 40, 41]. Different mutations of the *MICU1* gene have been reported [37–39]. Our patient showed mutation close to that reported by Musa et al. [42], [c.553C>T (p.Q185*)] a middle eastern founder mutation.

Patient 5 was diagnosed with MTP deficiency due to homozygous VUS of the *HADHB* gene. MTP is a multienzyme complex "formed of four alpha and four beta subunits" which is responsible for catalyzing the final three steps in beta-oxidation of long-chain fatty acids [42]. MTP is encoded by 2 genes, namely "*HADHA* and *HADHB*" [43]. Pathogenic variants in the *HADHB* gene are causative for MTP deficiency, an AR metabolic disorder of mitochondrial fatty acid oxidation [44]. It has diverse clinical manifestations, ranging from a severe lethal neonatal form with cardiomyopathy, hypoketotic hypoglycemia, sudden infant death [45], infantile-onset form with a hepatic Reye-like syndrome [46], late-onset neuromyopathic form with peripheral neuropathy, episodes of rhabdomyolysis [47] to mild myopathy [48, 49]. This phenotypic diversity is related to the defective fatty oxidation pathway, which is the major source of energy

for skeletal and cardiac muscles particularly during fasting, physical exertion or stress [50].

Although we detected VUS in the *HADHB* gene in our patient [c.397A>G p.(Thr133Ala)], his clinical presentation was matching the clinical profile reported in previous publications [48, 49]. There is some evidence suggesting that a strict dietary regimen consisting of low fat, high carbohydrate and medium-chain triglycerides (MCT) supplements might delay long-term cardiac and hepatic complications [44]. Our patient showed mild improvement with better exercise tolerance on dietary regimen and levocarnitine supplement; however, it was difficult to remain compliant.

Patient 6 was diagnosed with serine deficiency and GA-II, based on the detection of two missense homozygous VUS in *ETFDH*:p.Pro227Thr and *PHGDH*:p.Ser407Pro. Both variants were detected in a heterozygous state in parents, while only the *ETFDH* c.679C>A variant was detected in a heterozygous state in her healthy sibling. Therefore, the diagnosis was confirmed based on the patient's clinical presentation, auxiliary biochemical studies and the favorable response to treatment [10].

Serine deficiency is a rare AR disease caused by deficiency of one of the three enzymes, most commonly the "3-phosphoglycerate dehydrogenase (3-PGDH)" enzyme that is involved in serine metabolism. This will be manifested biochemically by low serine levels in the plasma and CSF [51]. The phenotypic spectrum ranges from a severe lethal form known as "Neu-Laxova syndrome" [52] to a milder form with nonspecific neurodevelopmental delay [53] depending on the residual enzymatic activity [52, 54]. Various neurological presentations have been reported including microcephaly, psychomotor regression, spasticity, seizures [55, 56] and cerebellar ataxia or adult progressive polyneuropathy [51].

GA-II, also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is an AR disease caused by homozygous or compound heterozygous mutations of *ETFA*, *ETFB* or *ETFDH* genes. This will lead to defects in electron transfer flavoprotein (ETF) or ETF dehydrogenase (ETFDH) with a resultant MAD insufficiency [57]. According to the position and nature of the identified variants position and the level of enzymatic activity [58], two forms of GA-II were described. The neonatal-onset severe form presents with or without congenital anomalies, respiratory failure, hypotonia, hypoglycemia and metabolic acidosis [59, 60]. The late-onset milder form presents with myopathic symptoms such as myalgia, muscle weakness and liver dysfunction [61].

Our patient showed an overlapping phenotypic spectrum in the form of muscle weakness, psychomotor regression, ataxia and refractory seizures. Complete cessation of seizures and remarkable improvement in the quality of life was achieved after receiving treatment. Identification of serine deficiency is essentially important knowing that it is a treatable disorder, unlike other neurometabolic disorders. Therefore, the appropriate dose of serine supplementation guided by biochemical correction of serine level is essential for better seizure control as shown in our patient [53].

Conclusions

After analyzing the phenotypic/genotypic spectrum of paroxysmal MDs of our patients, it was evident that early diagnosis is essential to identify treatable and potentially treatable pediatric MDs. Although we had a small number of patients, we were able to appreciate the effect of diagnosis-specific treatment on avoiding unnecessary medications, modifying the course of the disease and improving the quality of life of our patients.

Abbreviations

AADCD: Aromatic L amino acid decarboxylase deficiency; BFIC: Benign familial convulsions; EA: Episodic ataxia; GA-II: Glutaric aciduria type II; GLUT-1: Glucose transporter type 1 deficiency; ICCA: Infantile convulsions and paroxysmal choreoathetosis syndrome; MDs: Pediatric movement disorders; MPXPS: Myopathy with extrapyramidal signs; MTP: Mitochondrial trifunctional protein deficiency; N/R: Not reported; PKC: Paroxysmal kinesigenic choreoathetosis; SVD: Spontaneous vaginal delivery; VUS: Variant of uncertain significance.

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Author contributions

Dr. DAS is an assistant professor of Pediatrics at Faculty of Medicine, Ain Shams University; she is the principal investigator (PI) of the study and the corresponding author. She was responsible for designing the study, case selection, data collection, wrote the manuscript and analysed the data. Dr. AAA is an assistant professor of Department of Histology and Cell Biology, Faculty of Medicine, Ain shams University. Dr. AAA analysed and wrote the molecular data. All authors read, revised and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The ethical approval for this study was granted by the Institutional Review Board at the American Center for Psychiatry and Neurology in Abu Dhabi, UAE. An informed consent was obtained from all individual participants included in this study.

Competing interests

The authors declare that they have no competing interests.

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