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Comparison of lower extremity joint motion of children with different inborn errors of metabolism

Abstract

Objective: The purpose of this study is to investigate kinematic changes in children with IEMs.

Introduction: The diagnosis and treatment of inborn errors of metabolism (IEMs) can be challenging as clinical presentation is highly variable. Pathological gait in children with IEM may mistakenly be considered as one in CP.

Materials and Methods: Six children subsequently diagnosed with an IEM were referred for a standardized gait analysis and retrospectively recruited for a case series study. All of them were referred to have a gait analysis due to clinical impression with abnormal gait of cerebral palsy. Subjects were separated into three specific IEM conditions; Mitochondrial disease (MD), Carbohydrate-deficient glycoprotein syndrome (CDGS), or Glutaric acidemia type I (GA1).

Results: Children with MD or CDGS exhibited increased knee flexion and ankle dorsiflexion at initial contact and mid-stance phase, while the children with GA1 exhibited knee hyperextension and increased ankle plantarflexion at mid-stance. Toe off timing generally occurred later in the cycle for children with IEMs.

Conclusion: This indicates that the use of a gait analysis can assist clinicians' understanding of dynamic muscle spasticity and provide a functional outcome for different treatment options. Further gait analysis of children with IEMs is necessary to validate the observed findings and substantiate the use of standardized gait analysis as part of the clinical evaluation of a child with a suspected IEM.

Keywords: Inborn errors metabolism, Gait analysis, Muscle tone, Spasticity

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Abbreviations

IEM: Inborn Errors for metabolism, CP, Cerebral Palsy, TD, Typically Developing, PROM, passive range of motion (PROM), CDGS, Carbohydrate-deficient glycoprotein syndrome, MD, Mitrochondrial Disease, GA1, Glutaric acidemia type I

Introduction

Inborn errors of metabolism (IEMs) represent a heterogeneous group of genetic disorders, characterized by dysfunction of an enzyme or transport protein that results in either accumulation of a toxic product or lack of end product.[1] Clinical presentation is highly variable, as multiple organ systems are affected. Thus, pediatricians have been advised to pursue a diagnostic work-up for an IEM for any child with a clinical presentation including failure to thrive and either "neurologic symptoms" or myopathy.[2]

IEMs come in a large class from a variety of etiological factors. Mitochondrial disease (MD) is defined by the disruption of oxidative phosphorylation. Cells with high-energy requirements are preferentially vulnerable to limited ATP supply, particularly in neurons, skeletal and cardiac muscle.[3,4] Classic symptoms include progressive proximal myopathy with early exertional fatigue,myalgias, muscle cramps, contractures, and myoglobinuria.[3]

Carbohydrate-deficient glycoprotein syndrome (CDGS) is represented by a defect in the modification of glycoproteins by carbohydrates. CDGS is characterized by atrophy of the brainstem and cerebellum, and occasionally the cerebral cortex.[5] Common features include delayed development, hypotonia, ataxia, and mild facial dysmorphic features.[4-6]

Glutaric acidemia type I (GA1) is due to deficiency of glutaryl-CoA dehydrogenase. The accumulation of 3-hydroxyglutaric acid and glutaric acid results in striatal damage. There is a characteristic chronological pattern of acute dystonia, acute hypotonia with loss of head control, and increased tone to eventual rigidity and dystonia.[7]

For this preliminary study, we have observed six children, all who have been referred for gait analysis as part of this diagnostic "work-up." All of them were referred to the gait analysis due to clinical impression with abnormal gait of cerebral palsy. A review of the literature revealed gait patterns have not been previously described in this population. We hypothesize that children with IEM have a difference in kinematic function of the lower extremity as compared to typically developing children (TD). Thus, we present these six cases as a case-series study to explore the utility of standardized gait analysis as part of the clinical evaluation of a child with a suspected IEM and characterize the gait patterns.

Methods

Six children, subsequently diagnosed with an IEM (5 male, 1 female, mean age 10 years 6 months, age range 4-20 years), were referred for gait analysis. A total of twenty-four participants from our previous databases formed our TD group for comparison. These subjects compose of healthy, TD children who hold standard gait parameters and volunteered to participate in our studies. The data collection procedures of gait parameters for both study groups are identical. Specific reasons for referral to the IEM group were vague, including gait abnormality, variability of gait pattern, early fatigue, increased tone, and a diagnostic concern for cerebral palsy (CP). Inclusion criteria for the study include: 1) subsequent diagnoses of

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either MD, CDGS, or GA1; 2) had a full gait analysis and physical examination; 3) ability walk with or without an assistive device 4) no bias for age and gender.

Informed consent was obtained for each child and was approved by Institutional Review Board at the Children's Hospital of Wisconsin. The standardized gait analysis included a physical examination and acquisition of 3D joint rotations of the lower extremity. The physical examination included measurements of muscle strength, muscle tone (the modified Ashworth scale), anthropometric data and passive range of motion (PROM) at the ankle, knee, and hip joints.

Following the physical examination, sensors were placed on the posterior superior iliac spine, hip, knee, and foot of each child. Each child was instructed to walk barefoot at a self-selected speed across a level walking surface. Kinematic data was collected with the Electromagnetic Motion Tracking System (Polhemus Inc., Cochester, VT) for three adequate walking trials of at least 5 strides. Kinematic data included 3D motion of the ankle, knee, hip and pelvis as a function of one gait cycle. The muscle strength and tone, PROM, maximal flexion/extension, adduction/abduction and internal/external rotation of the joints in the lower extremity were measured and the descriptive data analysis were performed for both IEM and TD children using MATLAB software (The MathWorks, Inc., MA, USA).

Results

Participant demographics and physical examination findings are included in Table 1. Kinematic data from the six children with an IEM were compared to 24 TD age-matched controls. Repetitive gait analysis yielded a pronounced variation of gait patterns between trials for all children with IEMs relative to TD. The three children with MD and one child with CDGS exhibited increased knee flexion and ankle dorsiflexion at initial contact and mid-stance phase (Figure 1). The two children with GA1 exhibited knee hyperextension and increased ankle plantarflexion at mid-stance (Figure 2). Timing of toe-off varied between typically developing children (60% of gait cycle), MD (66.8%), CDGS (64.1%), and GA1 (61.9%).

Table 1 Subject demographics and selected physical examination findings (Mean).

	MD1	MD2	MD3	GA1	GA2	CDGS1
Diagnosis	MD	MD	MD	GA	GA	CDGS
Age (year)	4.3	20	13	13.2	4.3	8.2
Sex	F	M	M	M	M	M
Muscle Strength (5)						
Gluteus Maximus	3	2	3	3	4	1
Adductors	3	1.5	4	4	4	4
Medial Hamstring	3.5	4	4	4.5	4	3
Quadriceps	4	4	5	5	4	3
Anterior Tibialis	2	3.5	5	4	4	3
Gastrosoleus	5	2.5	5	2	3	2
Peroneus	2	2.5	5	4	3	3
Muscle Tone (0)						
Quadriceps	0.5	1	1	1	0	1
Hamstrings	0	1	3	0.5	0	1
Gastrosoleus	2	2.5	1	1	1.5	1
Peroneus	0	1	0	1	0	1
Range of Motion (°)						
KF (140-150)	155	152.5	148	141	150	147.5
KE (0)	0	-17.5	-2.5	9.5	9.5	0
DF1 (10-15)	14.5	-7.5	12.5	13.5	22.5	2.5
PF (50-60)	70	65	58.5	65	74	50
Eversion	16	8	0	9.5	12	8
Inversion	27.5	10	11	19	28	6
Special Range of Motion (°)						
SLR	67.5	21.5	29.5	57.5	70	52.5
Pop Angle (0-20)	15	64	70.0	45	22.5	37.5

MD: Mitochondrial Disease; GA: Glutaric Acidemia Type I; CDGS: Carbohydrate-Deficient Glycoprotein Syndrome; KF: Knee Flexion; KE: Knee Extension With Knee At 0 Degree; DF: Dorsiflexion of The Ankle With Knee At 0 Degree; PF: Plantarflexion of The Ankle; SLR: Straight Leg Raise Test; Pop: Popliteal; Normal Value In ( ).

Discussion

IEMs can present later in life with a more insidious picture of developmental delay or regression.[8] The six patients we observed were characterized by an insidious presentation with vague complaints from a parent or pediatrician. These complaints included observation of developmental delay or regression, increased tone, early fatigue, or variability of gait pattern. A common concern was the clinical similarity to cerebral palsy, especially if the patient had a complicated peri-natal course. A formal gait analysis was requested to characterize gait abnormalities and to assist with treatment recommendations. Gait analysis demonstrated gait characteristics that differed from typically developing children. In general, the gait patterns observed demonstrated increased variability between trials. Specific gait characteristic differences were observed in knee and ankle flexion / extension and appeared to be influenced by the specific IEM diagnosis.

The three children with MD were characterized by increased knee flexion and ankle dorsiflexion from initial contact to mid-stance (Figure 1). Increased knee flexion during stance phase has been attributed to one or more of the following: plantar flexor weakness, single joint hip extensor weakness, knee flexion contracture, or hamstring overactivity.[9] Two of the three children with MD demonstrated multiples of these characteristics; specifically plantar flexor and / or hip extensor weakness and knee flexion contractures (Table 1). However, the first child with MD (MD1) demonstrated none of these characteristics on physical examination (Table 1). In this case, we hypothesize that for this participant, hamstring overactivity may have contributed to the increased knee flexion. Particularly, it may be due to dynamic hamstring tone, which cannot be measured by physical examination technique. Static physical examination variables, specifically popliteal angle, have been demonstrated not to be reliable predictors of dynamic gait.[10] As a result of standardized gait analysis, each child's gait pattern was objectively characterized, leading to the prescription of appropriate orthotics (i.e. ground reaction AFOs).

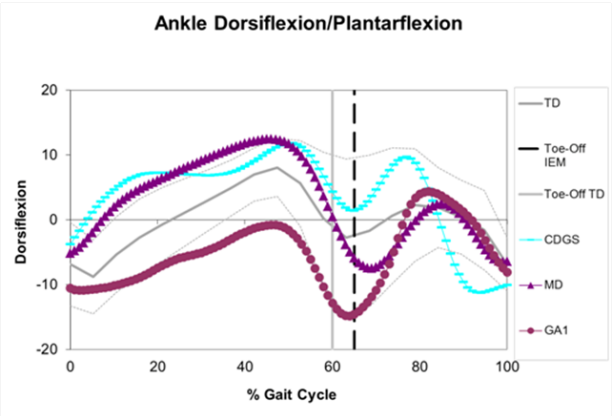

Figure 1 Ankle Dorsiflexion of healthy and separate IEM conditions.

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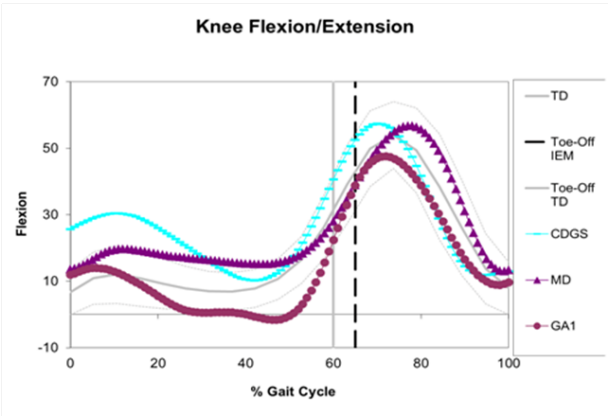

Figure 2 Knee flexion of healthy and separate IEM conditions.

The one child with CDGS demonstrated an even greater increased knee flexion (As compared to the MD group), and an increased ankle dorsiflexion from initial contact to mid-stance. In this child, muscle weakness was noted throughout, including the plantarflexors (2) and hip extensors (1) (Table 1). Hypotonia, developmental delay, and ataxia, are common features of CDGS, and may explain the observed gait pattern, as there was no evidence of either a knee flexion contracture or tone imbalance on physical examination. The standardized gait analysis of this child led to a similar clinical intervention as observed in the children with MD.

The two children with GA1 demonstrated increased knee extension and ankle plantar flexion at mid-stance. Knee hyperextension during stance phase has been attributed to one or more of the following: quadriceps weakness, plantar flexor weakness, quadriceps tone, or plantar flexor tone.[9] Abnormalities in tone are common in GA1, following a chronological pattern. In our study, one child's GA mildly increased plantarflexor tone (Table 1) likely contributed to the ankle plantarflexion and knee extension at mid-stance. Thus, standardized gait analysis in these two children with GA1 offered objective characterization of observed gait abnormalities, which led to appropriate initial orthotic recommendations, i.e. hinged AFOs.

Conclusion

This case-series study demonstrates that gait abnormalities may be encountered in children with different IEMs. The exact incidence of gait abnormalities in children with IEMs is not known. The six children we observed with gait abnormalities diagnosed with different IEMs represent an extremelfy small percentage of IEMs as a whole. However, in these six cases, representing three different diagnosis of IEMs, standardized gait analysis provided additional objective information that assisted in clinical decision making. As a result of this study, we are able to primarily demonstrate that pathological gait in children with IEM may mistakenly be considered as one in CP. Further gait analysis of additional children with IEMs is necessary to determine the generalizability of the observed findings, as well as substantiate standardized gait analysis as part of the clinical evaluation protocol in a child with a suspected IEM.

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Conflicts of interest

None.

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