Clinical Study
Exercise Stress Testing in Children with Metabolic or Neuromuscular Disorders

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The role of exercise as a diagnostic or therapeutic tool in patients with a metabolic disease (MD) or neuromuscular disorder (NMD) is relatively underresearched. In this paper we describe the metabolic profiles during exercise in 13 children (9 boys, 4 girls, age 5–15 yrs) with a diagnosed MD or NMD. Graded cardiopulmonary exercise tests and/or a 90-min prolonged submaximal exercise test were performed. During exercise, respiratory gas-exchange and heart rate were monitored; blood and urine samples were collected for biochemical analysis at set time points. Several characteristics in our patient group were observed, which reflected the differences in pathophysiology of the various disorders. Metabolic profiles during exercises CPET and PXT seem helpful in the evaluation of patients with a MD or NMD.

1. Introduction
Metabolic diseases (MDs) and Neuromuscular disorders (NMDs) comprise a large heterogeneous group of diseases, that directly (via intrinsic muscle pathology or defective metabolic pathways) or indirectly (via nerve pathology), impair muscle function and result in exercise intolerance.

Although the value of exercise tests in patients with MD/NMD has been acknowledged for several decades [1–3], the role of exercise stress tests as a diagnostic or evaluative tool in children and adults with MD/NMD is relatively underresearched. Moreover, exercise stress tests are not standard for most centers to be performed in clinical care [4–7]. In this paper, we provide two standardized exercise tests with preliminary metabolic profiles in children with a diagnosed MD/NMD for this purpose.

Exercise stress tests in patients with a metabolic disorder involved in ATP synthesis show a clear specific metabolic profile during exercise [4]. These metabolic profiles can be useful as a reference for identifying patients for a possible MD or NMD.

Therefore, the aim of the current study was to describe the metabolic profiles during exercise in children with a diagnosed NMD or MD. This information might be helpful for clinicians in the diagnosis and follow-up of patients with these disorders.

2. Methods
2.1. Subjects. In this retrospective chart review, patients with an established diagnosis involving general ATP synthesis or a dystrophinopathy, who were referred for exercise stress testing to the Departments of Metabolic Diseases and Child Development and Exercise Center, University Medical Center Utrecht, the Netherlands, were included.
Two exercise stress tests, respectively, were conducted to establish a diagnosis: a cardiopulmonary exercise test (CPET) and a prolonged exercise ergometry test (PXT). Following the morning breakfast, patients underwent a symptom-limited CPET on a bicycle ergometer. Workload was increased in constant increments of 10, 15, or 20 watts every minute, depending on the patient’s length of diagnosis and physical condition. This protocol was continued for three hours after the exercise test and further analyzed for lactate, creatine kinase (CK), ammonia, acylcarnitines, and organic acid. Urine samples were collected up to two hours after the exercise test and analyzed for creatinine, organic acid, amino acid, tetraglucose, purines, and pyrimidine [8].

Table 1: Cardiopulmonary measurements of patients during the CPET.

| Patient | Diagnosis | Determination of diagnosis | Age (years) | Sex | Weight (kg) | BMI (Z-score) | HRpeak (beats/min) | RERpeak | VO2peak (L/min) (Z-score) | VO2peak /kg (mL/min/kg) |
|---------|-----------|---------------------------|-------------|-----|-------------|---------------|-------------------|---------|--------------------------|-------------------------|
| 1       | GSD-1a    | Mutation R570X in delta F327 Debranching enzyme deficiency in leucocytes | 11.9        | M   | 40          | 19.3 (0.88)   | 205               | 1.16    | 1.99 (0.04)               | 49.7 (-0.42)           |
| 2       | GSD-III   |                          | 11.9        | F   | 39          | 19.6 (0.71)   | 182               | 0.92*   | 1.45 (1.5)                | 37.1 (-1.5)            |
| 3       | GSD-7     | Phosphofructokinase deficiency in muscle MCAD deficiency in leucocytes homozygous Lys329Glu mutation | 12.9        | M   | 32          | 13.1 (-3.7)   | 184               | 1.0     | 1.78 (-3.55)              | 34.6 (-3.24)           |
| 4       | MCAD      | MCAD deficiency in leucocytes | 5.4         | F   | 28          | 19.4 (1.98)   | 134               | 0.92*   | 0.55 (-3.5)               | 19.5 (-4.2)            |
| 5       | MADD      | MADD deficiency in fibroblasts | 11.4        | F   | 42          | 18.9 (0.59)   | NA                | NA      | NA                       | NA                     |
| 6       | SCAD      | SCAD deficiency in leucocytes and fibroblasts; mutation | 7.0         | M   | 25          | 14.6 (0.70)   | 173               | 1.05    | 1.00 (-0.86)              | 40.1 (-1.9)            |
| 7       | MADD      | MADD deficiency in fibroblasts | 10.2        | M   | 33          | 16.1 (-0.23)  | 195               | 1.25    | 1.33 (-1.1)               | 40.4 (-1.8)            |
| 8       | MADD      | MADD deficiency in fibroblasts | 8.6         | M   | 25          | 14.1 (-1.35)  | 180               | 1.21    | 1.29 (0.09)               | 51.5 (-0.26)           |
| 9       | GSD-III   | 2-Methylacetoacetyl-CoA-thiolase deficiency | 8.7         | M   | 30          | 15.5 (-0.32)  | 179               | 1.20    | 1.30 (-0.69)              | 43.5 (-1.4)            |
| 10      | M. Becker dystrophinopathy | Diminished ATP production in fresh muscle biopsy | 9.7         | M   | 34          | 16.9 (0.30)   | 152               | 1.39    | 0.63 (-3.6)               | 18.5 (-5.0)            |
| 11      | M. Becker dystrophinopathy | Duplication exon 24-29 dystrophin gene | 10.4        | M   | 25          | 12.4 (-3.6)   | NA                | NA      | NA                       | NA                     |
| 12      | M. Becker dystrophinopathy | Duplication exon 24-29 dystrophin gene | 14.8        | M   | 57          | 18.6 (-0.22)  | 202               | 1.26    | 1.57 (1.7)                | 62.6 (2.7)             |
| 13      | Hypokalemic episodic paralysis | Arg1239His mutation in CACNA1S-gene | 13.8        | F   | 62          | 24.5 (1.63)   | 218               | 1.25    | 1.20 (-2.0)               | 19.4 (-4.0)            |

Abbreviations: BMI: Body Mass Index, HRpeak: peak heart rate, VO2peak: peak O2 uptake, RERpeak: peak respiratory exchange ratio, *: significantly different from normal, NA: not assessed.

Thirteen patients (9♂, 4♀, age 5–15 years) with established diagnoses were studied in detail. Diagnoses were Glycogen Storage Disease (GSD) type 1a (1x), GSD type 3 (1x), GSD type 7 (1x), Medium-Chain Acyl CoA dehydrogenase deficiency (MCAD (2x)), Short-Chain Acyl CoA dehydrogenase deficiency (SCAD (1x)), Multiple Acyl CoA dehydrogenase deficiency (MADD (2x)), Debranching enzyme deficiency in leucocytes (1x), Mitochondrial respiratory chain myopathy (1x), Diminished ATP production in fresh muscle biopsy (1x), Duplication exon 24-29 dystrophin gene (1x), M. Becker dystrophinopathy (Becker Muscular Dystrophy (BMD) (2x)).

2.2. Exercise Tests. Two exercise stress tests, respectively, a cardiopulmonary exercise test (CPET) and a prolonged exercise ergometry test (PXT) were performed following a standardized protocol [8]. Blood samples were taken, immediately before and directly after the CPET and PXT, and analyzed for lactate, creatine kinase (CK), ammonia, acylcarnitines, and organic acid. Urine samples were collected up to three hours after the exercise test and further analyzed for creatinine, organic acid, amino acid, tetraglucose, purine, and pyrimidine [8].

A CPET (to determine the peak oxygen uptake [VO2peak] and peak workload [Wpeak]) and a submaximal PXT (90 minutes at 30% of Wpeak) were performed in the morning. After a light breakfast, the patients performed a symptom-limited CPET on a bicycle ergometer. Workload was increased in constant increments of 10, 15, or 20 watts every minute, depending on the patients’ length [9] and was in some conditions adjusted for the physical condition of the patient. This protocol was continued...
Table 2: Biochemical measurements of patients before and after the CPET.

| Patient | Lactate (mmol/L) | CK (U/L) | Ammonia (mmol/L) |
|---------|------------------|----------|------------------|
|         | Before | After | Before | After | Before | After | Before | After |
| 1       | 3.5*   | 10.3  | NA     | NA     | 5      | 4*    | NA     | NA    |
| 2       | 2.2    | 1.6   | 540*   | 597*   | NA     | NA    | NA     | NA    |
| 3       | 0.8    | 2.4   | 246*   | 273*   | 61*    | 337*  | NA     | NA    |
| 7       | 1.3    | 7.3   | 125    | 146    | NA     | NA    | NA     | NA    |
| 8       | 1.3    | 6.0   | 79     | 89     | NA     | NA    | NA     | NA    |
| 9       | 1.5    | 4.3   | 116    | 121    | 17     | 12    | NA     | NA    |
| 10      | 3.1*   | 6.9   | 85     | 100    | 8      | 6*    | NA     | NA    |
| 12      | 1.5    | 13*   | 577*   | 773*   | 34*    | 54    | NA     | NA    |
| Normal values | 1.56  | 7.0   | 104    | 123    | 18     | 42    | NA     | NA    |
| Mean (range) | (0.7–2.3) | (3.2–11.4) | (45–192) | (51–234) | (9–23) | (10–94) | NA     | NA    |

Legend: NA: not assessed, *: significantly different from normal.

3. Results

3.1. CPET. As expected, patients with a MD/NMD showed abnormal results on the CPET (Tables 1 and 2). Patient 2 (GSD-3) stopped the CPET because of myalgia in the lower limbs, compared to reference values for healthy children [10, 11], the patients with GSD-3, MCAD, SCAD, and mitochondrial myopathy (patients 4, 6, and 10, resp.) had a significantly reduced HRpeak. RERpeak was significantly lower in the patient with GSD-3 (patient 2) and also increased to 1.0 in the patient with GSD-7 (patient 3). VO2peak and VO2peak/kg were significantly lower in the patients 3, 4, 10, and 13. These were patients with GSD-7,
Table 3: Biochemical measurements of patients during the PXT test.

| Subject | Time (min) | Glucose (mmol/L) | Lactate (mmol/L) | FFA (mmol/L) | 3-Keto-B (mmol/L) | 3-OH-B (mmol/L) | CK (U/L) | Ammonia (µmol/L) |
|---------|-----------|-----------------|-----------------|-------------|-----------------|-----------------|---------|------------------|
| 1       | 0         | 4.9             | 4.3*            | 0.51        | 0.14            | 0.0             | 116     | 166              |
|         | 30        | 4.4             | 4.6*            | 0.52        | 0.13            | 0.02            | 115     |                  |
|         | 60        | 5.7*            | 2.8*            | 0.489       | 0.12            | 0.02            | 119     |                  |
|         | 75        | 5.6             | 3.1*            | 0.536       | 0.12            | 0.02            | 119     |                  |
|         | 90        | 6.7*            | 2.9*            | 0.559       | 0.12            | 0.02            | 121     |                  |
|         | 15 after  | 7.4*            | 4.1*            | 0.792       | 0.13            | 0.04            | 121     |                  |
|         | 30 after  | 7.5*            | 4.9*            | 0.666       | 0.12            | 0.04            | 118     |                  |
| 3       | 0         | 5.5             | 1.8             | 0.08        | 0.0             | 0.0             | 181*    | 184*             |
|         | 30        | 5.9             | 1.2             | 0.14        | 0.0             | 0.0             | 186*    |                  |
|         | 60        | 5.8*            | 0.8             | 0.23        | 0.0             | 0.0             | 187     | 275*             |
|         | 75        | 6.9*            | 1.2             | 0.36        | 0.09            | 0.03            | 183*    |                  |
|         | 15 after  | 6.9             | 2.3             | 0.25        | 0.0             | 0.0             | 184*    | 144*             |
|         | 30 after  | 2.0             | 0.26            | 0.0         | 0.0             | 0.0             | 51      |                  |
| 6       | 0         | 4.6             | 3.2*            | 0.268       | 0.12            | 0.0             | 48      |                  |
|         | 30        | 4.6             | 1.3             | 0.302       | 0.1             | 0.0             | 46      |                  |
|         | 60        | 4.4             | 1.4             | 0.444       | 0.12            | 0.0             | 48      |                  |
|         | 15 after  | 4.6             | 1.1             | 0.503       | 0.13            | 0.03            | 51      |                  |
|         | 30 after  | 4.7             | 0.9             | 0.528       | 0.13            | 0.03            | 117     |                  |
| 7       | 0         | 7.1             | 1.1             | 0.76        | 0.07            | 0.09            | 103     |                  |
|         | 30        | 5.6             | 1.2             | 0.28        | 0.0             | 0.0             | 0.0     |                  |
|         | 60        | 4.9             | 1.0             | 0.49        | 0.0             | 0.0             | 98      |                  |
|         | 75        | 4.8             | 1.3             | 0.88        | 0.05            | 0.05            | 105     |                  |
|         | 90        | 5.5             | 1.1             | 1.03        | 0.10            | 0.12            | 119     |                  |
|         | 30 after  | 4.8             | 1.0             | 0.93        | 0.15            | 0.26            | 117     |                  |
| 8       | 0         | 5.2             | 2.0             | 0.15        | 0.0             | 0.0             | 58      |                  |
|         | 30        | 4.6             | 0.9             | 0.31        | 0.0             | 0.0             | 0.0     |                  |
|         | 60        | 4.3             | 0.9             | 0.62        | 0.07            | 0.04            | 80      |                  |
|         | 75        | 4.4             | 1.0             | 0.91        |                |                | 78      |                  |
|         | 30 after  | 4.5             | 1.2             | 1.34        | 0.14            | 0.24            | 78      |                  |
| 9       | 0         | 6.4             | 1.4             | 0.22        | 0.09            | 0.03            | 90      | 14               |
|         | 30        | 4.9             | 1.4             | 0.18        | 0.0             | 0.0             | 93      |                  |
|         | 60        | 4.7             | 1.3             | 0.21        | 0.0             | 0.0             | 89      |                  |
|         | 75        | 4.4             | 1.1             | 0.42        | 0.0             | 0.0             | 99      | 22               |
|         | 90        | 4.9             | 1.1             | 0.64        | 0.11            | 0.11            | 91      |                  |
|         | 15 after  | 4.8             | 0.8             | 0.69        | 0.13            | 0.18            | 92      |                  |
|         | 30 after  | 4.6             | 1.0             | 0.55        | 0.14            | 0.2             | 92      | 14               |
| 10      | 0         | 4.0             | 2.4*            | 0.20        | 0.11            | 0.10*           | 138     | 20               |
|         | 30        | 3.7*            | 8.6*            | 0.21        | 0.11            | 0.11*           | 156     |                  |
|         | 60        | 3.5*            | 9.6*            | 0.31        | 0.14            | 0.13            | 151     |                  |
|         | 75        | 3.6*            | 9.5*            | 0.49        | 0.16            | 0.16            | 156     | 20               |
|         | 90        | 3.6*            | 9.7*            | 0.71        | 0.16            | 0.18            | 157     |                  |
|         | 15 after  | 4.1             | 7.0*            | 0.72        | 0.113           | 0.29            | 145     |                  |
|         | 30 after  | 4.0             | 4.7*            | 0.73        | 0.18            | 0.29            | 146     |                  |
| 11      | 0         | 5.9             | 1.4             | 0.41        | 0.0             | 0.0             | 5020*   | 7.0              |
|         | 30        | 4.8             | 1.4             | 0.19        | 0.0             | 0.0             | 4975*   |                  |
|         | 15 after  | 5.3             | 1.4             | 0.57        | 0.0             | 0.0             | 5036*   |                  |
|         | 30 after  | 5.2             | 1.3             | 0.5         | 0.0             | 0.0             | 18      |                  |
MCAD, mitochondrial myopathy, and Hypokalemic episodic paralysis, respectively.

A remarkably high VO\textsubscript{2peak/kg} was observed in one of the patients with BMD (patient 12).

The patients with GSD-1a and mitochondrial myopathy (patient 1 and 10, resp.) had significantly increased lactate concentrations at rest. Patient 2, with GSD-3, had an increased CK values at rest and after exercise. The 2 patients with BMD (patients 11 and 12) showed persistently highly elevated CK levels. One patient (patient 13) showed mildly elevated CK.

### 3.2. PXT.

Biochemical profiles of the MD/NMD patients during the PXT varied with the disorder (Table 3). Two patients, one with GSD-1a and the other with mitochondrial myopathy (resp., patient 1 and 10), showed significantly increased concentrations of blood lactate at all time points. The patient, with GSD-7 had significantly increased ammonia concentrations with no rise in lactate during exercise.

During and after exercise, the CK value of the patient with GSD-7 (patient 3) was significantly increased as well as in the 2 patients with BMD (patients 11 and 12).

Acylcarnitines C6, C8, C10, C12, and C14:1 were all increased in two patients with MADD (patients 7 and 8) in rest as well as during exercise. The patient with ketothiolase deficiency (patient 9) had increased C5:1 and C5-OH acylcarnitine during rest and exercise, as well as several increased organic acids in the urine. In the patient with mitochondrial myopathy (patient 10), C5 carnitine was increased in the urine during and after exercise. In the patient with SCAD (patient 6), there was no C4 carnitine found. In all other MD/NMD patients, no altered acylcarnitines, carnitines, for organic acids concentrations could be observed in plasma or urine (data not shown).

### 4. Discussion

The purpose of this study was to describe metabolic profiles during exercise using CPET and PXT including extensive blood and urine analyses in children with a diagnosed MD/NMD. This information might be helpful for clinicians in the diagnosis and follow-up of these disorders. Because of the heterogeneity of the disorders, there was a large variation in the CPET and PXT results between patients. These differences reflect the different pathophysiology of the various disorders (e.g., defects in different metabolic pathways) and heterogeneity within disorders.

Metabolic profiling might be helpful in the further workup towards a diagnosis. For example, a low rise in lactate after CPET is suggestive for a GSD, and a very high increase in lactate, combined with a very low VO\textsubscript{2peak}, might be suggestive for a mitochondrial myopathy. Further studies should develop an algorithm for the interpretation of exercise data in MD/NMD patients, comparable to the interpretative algorithms for cardiac and pulmonary limitations during exercise [12, 13].

The diagnostic yield of exercise stress testing in children with unexplained exercise intolerance seems relatively low. Among 29 patients referred for exercise intolerance of unknown origin, only 3 patients could be diagnosed with a MD/NMD: 2 patients with a Becker Muscular Dystrophinopathy and one patient with a hypokalemic episodic paralysis. However, many of these patients have undergone extensive medical screening before they were referred for exercise testing. Ten percent is therefore a reasonable yield. It is our opinion that the expense of exercise testing including extensive blood and urine analyses is justified because it could be useful for guiding the diagnostic workup and can differentiate between patients with medically unexplained exercise intolerance and patients with a MD/NMD. In patients with a MD involved in ATP synthesis, only during certain periods of metabolic stress (e.g., exercise, fasting, or illness), abnormal quantities of metabolites in blood and urine can be found, and symptoms are present. These defects can only be indentified using standardized tests. The current paper provides two standardized exercise tests with preliminary metabolic profiles for this purpose.

Furthermore, several of the tested MD/NMD patients (patients 3, 7, 8, and 10) were referred for exercise testing to assess their exercise capacity for physical activity recommendations. Based on their exercise results, an advice regarding appropriate levels of physical activity was provided. Sufficient amounts of physical activity are necessary for an optimal physical, psychosocial, and emotional development in children [14].

In addition, for patient 12, we gave an exercise restriction based on the findings. This patient was a talented cyclist with a very high VO\textsubscript{2peak} for his age. However, during several races he developed myoglobinuria, and he had quite high resting values of CK. A muscle biopsy in the workup after the tests

### Table 3: Continued.

| Subject | Time (min) | Glucose (mmol/L) | Lactate (mmol/L) | FFA (mmol/L) | 3-Keto-B (mmol/L) | 3-OH-B (mmol/L) | CK (U/L) | Ammonia (µmol/L) |
|---------|------------|------------------|------------------|-------------|------------------|----------------|---------|------------------|
| 12      | 0          | 5.1              | 1.1              | 0.15        | 0.0              | 0.0            | 695     | 33               |
|         | 30         | 5.3              | 1.2              | 0.08        | 0.0              | 0.0            | 776     |                  |
|         | 60         | 5                | 1.2              | 0.11        | 0.0              | 0.0            | 774     |                  |
|         | 75         | 5.1              | 1.4              | 0.16*       | 0.0              | 0.0            | 771     | 51               |
|         | 90         | 5.0              | 1.7              | 0.23        | 0.0              | 0.0            | 766     |                  |
|         | 15 after   | 5.1              | 1.1              | 0.76        | 0.0              | 0.0            | 755     |                  |

 Legend: FFA: free fatty acids, 3-keto-B: 3-ketobutaric acid, 3-OH-B: 3-hydroxybutaric acid, *: significantly different from normal.
revealed a duplication in exon 24–29 of the dystrophin gene, and the diagnosis of BMD was made. Based on these results, the boy was advised to stop high-level cycling because of the increased risk of renal failure due to myoglobinuria.

One of the limitations of this clinical report is the small and heterogeneous population. This reflects the rarity of the disorders. Therefore, multicentred studies are needed to increase the sample size for each of the disorders. Further, it is important that these profiles are established in children as not all metabolic profiles seen in adults are valid in children. For example, a recent study showed that the well-known second-wind phenomenon in patients with McArdle’s disease (GSD5), which is considered as a diagnostic feature of this disease [15], was not observed in children with McArdle’s disease [16].

5. Conclusion
In this paper we describe the metabolic profiles during exercise in 13 children with a diagnosed MD/NMD. Metabolic profiles during exercise were of assistance in diagnosing 3 patients with rare presentations of MD/NMDs. In addition, exercise stress testing was helpful for the prescription of appropriate levels of physical activity.

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