The Exercise Test in Andersen Syndrome

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**Background:** Andersen syndrome is a rare form of periodic paralysis (PP) associated with dysmorphic features and potentially fatal cardiac dysrhythmias. To date, no electrodiagnostic abnormalities have been reported that can be used to confirm the presence of PP in this condition.

**Objectives:** To determine if the exercise test could be used to confirm the diagnosis of PP in Andersen syndrome. To evaluate the exercise test as a means to assess neuromuscular status during treatment.

**Methods:** We performed the exercise test on 2 patients with Andersen syndrome. In 1 patient, we used a modified version of the test to document responsiveness to treatment with tocainide.

**Results:** Studies in both patients demonstrated a progressive decline in the compound muscle action potential amplitude after exercise that was characteristic of the phenomenon seen in other forms of PP. In 1 patient, improvement in interattack strength and a reduction in the number of attacks of weakness correlated with improvement in the test results.

**Conclusions:** Our cases demonstrate that the exercise test can confirm the diagnosis of PP in Andersen syndrome. A modified version of exercise testing may also be considered as an objective method for documenting treatment responses in PP.

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KLEIN et al in 1962 and Lisak et al 8 years later were the first authors to describe the simultaneous occurrence of periodic paralysis (PP) and cardiac dysrhythmia. 3-7 In 1971, Andersen et al described an 8-year-old boy with a distinct syndrome marked by the clinical triad of PP, cardiac dysrhythmia, and developmental anomalies. The full triad was reported only once more before 2 recent case series brought attention to this rare condition, now termed Andersen syndrome (AS).

Sansone et al emphasized that in AS, the potassium shifts during attacks of paralysis are inconsistent, and traditional classifications of hypokalemic, normokalemic, or hyperkalemic PP cannot be applied. The attacks are often superimposed on a background of generalized weakness. Cardiac abnormalities may be limited to a long QTc interval, but dangerous rhythms including biventricular tachycardia and cardiac arrest occur in some individuals. The inheritance pattern appears to be autosomal dominant with significant phenotypic heterogeneity. Tawil et al excluded genetic linkage to loci for hyperkalemic PP on chromosome 17 and to the long QT syndrome locus on chromosome 11. Linkage studies to 3 other long QT loci were also negative, while mutational analysis of the dihydropyridine receptor gene for hypokalemic PP was unremarkable. Treatment for AS remains empirical and is frustrated by a paradoxical response of cardiac and skeletal muscle to changes in potassium levels, unpredictable responses to drugs, and an overall refractoriness to antiarrhythmic agents.

To date, no electrodiagnostic abnormalities have been reported that confirm the presence of PP in AS. We were interested in determining if the “exercise test” could be used for this purpose. The exercise test was described by McManis et al as a simple electrodiagnostic method to confirm clinical suspicion when the diagnosis of PP was uncertain. McManis et al studied 21 patients with clinically definite hyperkalemic PP, normokalemic PP, or hypokalemic PP, and compared these patients with a group of healthy individuals. Most patients with PP had a greater than normal increase in the compound muscle action potential (CMAP) amplitude immediately after 2 to 5 minutes of intermittent voluntary contraction. This was followed over the next 30 to 40 minutes by a progressive decline in CMAP amplitude to well below the preexercise baseline. Patients with hyperkalemic PP, on average, had much greater amplitude increments and decrements than patients with hypokalemic PP, but there was overlap between individual patients.

Because the exercise test has not been reported in AS, we undertook a study to document the electrodiagnostic changes that fol-
METHODS

We stimulated the ulnar nerve at the wrist and recorded CMAPs from the abductor digitii minimi. The CMAPs were recorded every 60 seconds for 2 minutes prior to exercise to ensure a stable baseline. Exercise was performed for 3 minutes by having the patient forcefully abduct the fingers against resistance with 3- to 5-second rest periods every 15 to 20 seconds. We recorded the CMAP immediately following exercise and every minute thereafter until there was no change for at least 3 minutes. We calculated the percentage change in amplitude using the following formulas:

\[
\frac{\text{Peak Amplitude After Exercise} - \text{Baseline Amplitude Before Exercise}}{\text{Amplitude Before Exercise}} \times 100\%
\]

\[
\frac{\text{Peak Amplitude After Exercise} - \text{Smallest Amplitude After Exercise}}{\text{Peak Amplitude After Exercise}} \times 100\%
\]

If the CMAP amplitude declined during the exercise period, we calculated the percentage decrement by substituting the baseline amplitude for the peak amplitude after exercise.

Based on 14 control subjects used in the series by McManis et al., we set normal limits for the CMAP amplitude decrement at 40% and for the amplitude increment at 30%. Values greater than these normal limits were considered to be consistent with PP.

Finally, to compare the sequential tests in patient 1, we used the following formula:

\[
\frac{\text{Baseline Amplitude Before Exercise} - \text{Amplitude at 10 to 20 Minutes After Exercise}}{\text{Baseline Amplitude Before Exercise}} \times 100\%
\]

REPORT OF CASES

PATIENT 1

A 27-year-old woman was referred for evaluation of periodic weakness. The episodes of weakness started at low exercise with 2 previously described patients. In addition, given that treatments in AS are unpredictable and empirical, we sought to determine if the exercise test could be used as an adjunct to patient reporting for documenting therapeutic responses. To do so, we applied a modified version of the exercise test. We want to bring attention to this new application, which may also be useful for documenting and comparing treatment responses in other forms of PP. Our results and the potential pitfalls of using our method are discussed.

Figure 1. Patient 1. Characteristic facial features of Andersen syndrome including hypertelorism, hypoplastic mandible, and low-set ears.

4 years of age and initially occurred once to twice per month. At 8 years of age, serum creatine kinase level and muscle biopsy findings were normal. The serum potassium level was in the high normal range during an attack (4.7 mmol/L). The attacks increased from 4 to 6 episodes monthly in recent years lasting 3 to 24 hours. The patient also reported generalized weakness at baseline for the last 3 years.

She was first evaluated for dysmorphic facial features at the age of 19 months. A routine physical examination at 9 years of age documented the presence of a cardiac dysrhythmia and at 10 years of age she had her first of 4 episodes of nonfatal cardiac arrest. A diagnosis of long QT syndrome was made (QTc = 0.56 seconds, normal <0.43). She received 600 mg of quinidine daily and 80 mg of propranolol daily. She had no further cardiac symptoms until a syncopal episode occurred at 26 years of age, at which time therapy with these medications was discontinued. The patient was adopted and has no known siblings. From the history that is available, the mother was of short stature and the maternal grandmother died of a heart attack at 43 years old.

Examination revealed a 4 ft 11 in woman with a high arched palate, hypertelorism, a hypoplastic mandible, low-set ears, and clinodactyly of the fifth digits (Figure 1). Between attacks of weakness, cranial nerves were intact without ptosis or facial weakness. Muscle strength testing was Medical Research Council grade 4 strength proximally and distally in the upper and lower extremities. Sen-
Tendin reflexes were hypoactive. During an attack of paralysis, strength was grade 3 proximally and distally with areflexia.

Holter monitoring demonstrated frequent premature ventricular contractions. Measurements of serum electrolytes and creatine kinase level at baseline were normal. Hyperkalemia, provoked by oral administration of potassium, abolished ventricular ectopy with a level of 7.0 mmol/L and did not cause weakness. Oral treatment with 40 mEq of potassium daily and 375 mg of acetazolamide daily had no effect on strength or on ventricular ectopy.

The patient was treated with 600 mg of tocainide daily. Tocainide reduced the frequency of PP from 1 to 2 episodes per month and improved the interattack weakness. However, a syncopal episode occurred 12 months after therapy was initiated. Repeated Holter monitoring showed a marked increase in the frequency of the ventricular dysrhythmia with runs of ventricular tachycardia lasting up to 122 beats at rates of up to 170/min and periods of bigeminal rhythm. She did not report any symptoms during the period of monitoring. Based on this study, the use of tocainide was discontinued. The attacks of weakness increased to 6 per month. A repeated Holter monitor showed improvement in the degree of ventricular ectopy.

PATIENT 2

A 16-year-old boy was evaluated for attacks of weakness. The attacks began at 14 years of age, lasted for 1 to 4 days, and occurred once per week on average. The weakness tended to be maximal on awakening and would resolve over the course of the day. Evaluation shortly after the initial episode revealed normal electromyography, muscle biopsy findings, and serum creatine kinase level.

Runs of ventricular tachycardia were first recorded at 7 years of age on a routine electrocardiogram. He was treated with amiodarone; treatment was discontinued when he developed symptomatic bradycardia. He subsequently received treatment with 150 mg of flecainide daily and had a pacemaker placed. His cardiac symptoms have not recurred for the last 9 years. There was no family history of cardiac abnormalities or weakness.

Examination revealed short stature (5 ft 3 in), low-set ears, micrognathia, short index fingers, clinodactyly, and low-set thumbs. Cranial nerves were normal without facial weakness. Muscle strength at baseline was Medical Research Council grade 4 proximally and distally. Deep tendon reflexes were intact. During a PP attack, strength was grade 2 proximally and grade 4 distally, and he was areflexic. The QTc interval when treatment with flecainide was discontinued was 0.48 seconds (normal <0.42 seconds).

Laboratory evaluations during several attacks of weakness demonstrated normal, increased, or decreased potassium levels ranging from 2.7 to 5.2 mmol/L. He was maintained on a regimen of flecainide for the cardiac arrhythmia. Empirical trials of several medications, including 60 mg of propranolol daily, 150 mg of dichlorphenamide daily, and 375 mg of acetazolamide daily were not associated with any notable benefits or worsen-
Exercise of individual groups of muscles followed by rest can induce focal weakness in all forms of PP. Regardless of the underlying molecular mechanisms, during an attack of weakness the muscle fiber surface membrane depolarizes and becomes inexcitable to direct and indirect stimulation. A CMAP amplitude reduction is an electrodiagnostic correlate of this fiber inexcitability and serves as the basis for the exercise test. Most patients with PP also develop an abnormal transient increase in the CMAP amplitude immediately after exercise, particularly when the baseline amplitude is low. Although the exact mechanisms are unclear, in hyperkalemic PP the increase may pertain to a transient protective effect of acidosis, as would be induced by exercise.

In both of our patients, the exercise test demonstrated the CMAP amplitude decrements of at least 40% that are also seen in hyperkalemic and hypokalemic PP. The CMAP declines resulted in values that were well below the pretest baseline, a feature that also supports the diagnosis of PP and can be contrasted with normal controls where CMAP amplitudes fall only to or slightly below the pretest baseline. The increments and decrements in our patients with AS were similar in magnitude although they occurred somewhat more rapidly than in the subgroup of patients with hypokalemic PP reported by McManis et al. This is in contrast to patients with hyperkalemic PP who showed increments and decrements of greater magnitude that occurred with similar timing to our patients with AS (Table 2).

In a patient with thyrotoxic hypokalemic PP, Jackson and Barohn demonstrated that abnormalities on the exercise test and the episodes of PP both resolved fol-

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Table 1. Effect of Treatment on the Exercise Test in Patient 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Baseline CMAP Amplitude, mV</th>
<th>Immediately After Exercise CMAP Amplitude, mV</th>
<th>Increment, %</th>
<th>Decrement, %</th>
</tr>
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<tr>
<td>1</td>
<td>None</td>
<td>7.43</td>
<td>7.47</td>
<td>0.6</td>
<td>22.3</td>
</tr>
<tr>
<td>2</td>
<td>Tocainide</td>
<td>7.86</td>
<td>10.17</td>
<td>23.3</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>5.83</td>
<td>7.57</td>
<td>29.8</td>
<td>16.8</td>
</tr>
</tbody>
</table>

*CMAP indicates compound muscle action potential.
lowing thyroid ablation. We were interested in using the exercise test to objectively document changes with treatment in our patient. To calculate amplitude decrements, McManis et al13 used the peak CMAP amplitude after exercise and the postexercise nadir CMAP amplitude and did not control for time. This yields the absolute magnitude of the CMAP change during testing, but it does not allow for comparisons of how readily the CMAP amplitude declines. We modified the exercise test protocol for the purpose of comparing sequential studies. Given that CMAP amplitudes correlate with strength in PP,13 we compared CMAP amplitudes at fixed times after exercise with the pre-exercise amplitude as an electrophysiologic estimate of how readily weakness was induced by exercise.

Tocainide is a class 1 cardiac antiarrhythmic agent that depresses the fast-inward sodium current, thereby lengthening the refractory period and delaying the return of membrane excitability.16 Tocainide blocks the stiffness and transient weakness associated with myotonia congenita16,18 and prevents weakness induced by cooling in paramyotonia congenita.19 However, the ability to improve periodic weakness, as observed in patient 1, has not been reported. The positive response was interesting given that AS is not caused by a genetic abnormality in the sodium channel. This points out that a drug can be effective in PP even if it does not reverse the primary channel defect. A more common example is carbonic anhydrase inhibitors that can benefit patients with both hypokalemic and hyperkalemic PP.20,21 By comparing decrements during treatment with tocainide to the pretreatment and posttreatment values, it was evident that tocainide led to a reduction in the magnitude of the CMAP amplitude decline at fixed times after exercise. The results of electrodiagnostic testing correlated with the reduced frequency of attacks reported by the patient during therapy, and indicate that the use of tocainide protected against the underlying pathophysiological derangement that ultimately led to the attacks of paralysis.

It is important to note that factors such as the time of day, temperature, serum potassium levels, and recent meals may affect the susceptibility of muscle to exercise in PP.13 Day-to-day variability may be present in a given individual,13 creating a need for caution in comparing the results of exercise tests. Although a consistent relationship between any single factor and its effect on muscle excitability has not been shown in AS, it is still possible that phenomena other than treatment could have influenced our results. To control the testing as well as possible, we administered 3 identical studies to our patient in the early afternoon. We also demonstrated that repeated testing, after treatment with tocainide was discontinued, yielded virtually identical results to the study prior to initiating treatment. Moreover, the results of all 3 studies showed remarkable consistency with the patient’s overall neuromuscular status.

Our study indicates that the exercise test can confirm the presence of PP in AS as it does in other variants of PP. Our findings also suggest that serial testing with a modified exercise test may complement patient reporting and serve as an objective means to document the neuromuscular status of individual patients with AS. It is possible that adapting the exercise test to measure CMAP declines at fixed times after exercise will allow it to be used as a measure of therapeutic effectiveness in other forms of PP.

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