Response of Motor Complications in Cockayne Syndrome to Carbidopa-Levodopa

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Background: Gait difficulties, tremors, and coordination difficulties are common features of Cockayne syndrome that are consequences of leukodystrophy, cerebellar atrophy, and demyelinating neuropathy, but no pharmacotherapy for these disabling symptoms is available.

Objective: To determine whether carbidopa-levodopa relieves tremors and other motor complications of Cockayne syndrome.

Design: Mutation analysis and case report study.

Setting: Hospital clinic and genetics research laboratory.

Patients: We studied 3 patients with Cockayne syndrome, a rare autosomal recessive neurodegenerative disorder for which no known treatments are available.

Intervention: Carbidopa-levodopa therapy.

Main Outcome Measures: Status of tremors, ability to perform daily tasks, serial physical examinations, and results of handwriting samples.

Results: All 3 patients had a clear reduction in tremors and improvements in handwriting and manipulation of utensils and cups.

Conclusions: Patients with Cockayne syndrome should be evaluated carefully for movement disorders. A clinical trial should be considered to evaluate this therapy further.

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Cockayne Syndrome (CS) is a rare autosomal recessive neurodegenerative disorder caused by mutations in ERCC8 (CSA or CKN1) and ERCC6 (CSB). The clinical phenotype of CS is distinctive and includes microcephaly, intellectual disability, short stature, cutaneous photosensitivity, pigmentary retinopathy, cachexia, premature aging, and deafness.

The pathophysiologic features involve a defect in nucleotide excision repair (NER), a process that reverses a range of DNA helix-distorting lesions, including damage caused by UV radiation. Cockayne syndrome is classified as an NER disorder, along with xeroderma pigmentosum, which is characterized by severe cutaneous photosensitivity and a high risk of skin cancer, and trichothiodystrophy, which is associated with photosensitivity, poor growth, neurodegeneration, and brittle hair.

Gait difficulties, tremors, and coordination difficulties are common features of CS that are consequences of leukodystrophy, cerebellar atrophy, and demyelinating neuropathy, but no pharmacotherapy for these disabling symptoms is available. Among patients enrolled in a genetic study of CS, we studied 3 adolescents with a relatively mild course who had clear tremors and motor difficulties.

Methods

The setting was a hospital clinic and genetics research laboratory. Patients and their parents were enrolled in a research study of the genetics of CS following an approved protocol of the Children's Hospital Boston, and informed written consent was obtained. Mutation analysis of the ERCC8 (CSA) and ERCC6 (CSB) genes was performed by direct DNA sequencing of the coding exons and their flanking splice junctions on a DNA analyzer (ABI Prism DNA Analyzer; Applied Biosystems, Foster City, California). Control DNA samples were obtained anonymously from 96 patients unaffected by CS. Three patients with CS identified through this genetic study were given therapeutic trials of carbidopa-levodopa on a clinical basis.

Results

Patient 1

A 13-year-old, right-handed girl with CS had increased muscle tone in the lower extremities (left greater than right) since the...
age of 15 months. Her parents first observed bilateral hand tremors at 3 or 4 years of age. She has an unsteady gait and difficulty with motor tasks, including writing, holding beverages, buttoning, zipping, and putting on socks and shoes. She uses training wheels on her bicycle.

Physical examination findings revealed bilateral heel cord contractures, jerky ocular pursuits, and dysmetric saccades. Fluctuating dystonia was present in both legs, with mild distal weakness. Tendon stretch reflexes were diminished in the arms and at the patellae and absent at the ankles, with flexor plantar responses. Vibration sensation was diminished. Bilateral intention tremors were present, with dysmetria and dysdiadochokinesia, but she had neither a postural or resting tremor. She navigated stairs with mild difficulty and some bradykinesia. Further clinical details are given in Table 1. Motor nerve conduction studies of the right tibial nerve recording abductor hallucis brevis demonstrated slowing of nerve conduction, with a latency of 6.7 milliseconds (reference range, <5.7 milliseconds), an amplitude of 5.9 mV with ankle stimulation and 3.1 mV with popliteal stimulation (reference range, >2.8 mV), and a velocity of 26 m/s (reference range, >41 m/s). F-response latency was 40 milliseconds (reference range, <56 milliseconds). Bilateral sural sensory responses were absent.

Mutation analysis demonstrated inheritance of 2 compound heterozygous CSA mutations by this patient: c.37G>T (p.E13X), a nonsense mutation inherited from the father that was previously reported in an unrelated patient with CS7; and IVS11-1G>C, a novel splice acceptor mutation inherited from the mother that alters the invariant AG dinucleotide (Figure 1A and B). Neither mutation was present in the control samples. The results of genetic testing for GCH1 were negative, excluding the classic form of dopa-responsive dystonia.

A combination of carbidopa, 25 mg, and levodopa, 100 mg, was prescribed at initially a half tablet by mouth twice a day and then increased to 1 tablet twice a day. Approximately 1 week after starting the full dose, she and her parents noticed a reduction in her tremors, improvement in her handwriting, and better manipulation of utensils. Eight weeks after the initial visit, her handwriting sample showed marked improvement (Figure 2A and B), her hypertonia had improved, and her dysmetria had diminished, with a significant beneficial effect on her schoolwork.

**Patient 2**

A 14-year-old boy with CS had significant tremors that limited his activities of daily living. He had poor feeding through the first year of life. Acquired microcephaly was observed at the age of 14 months. He was diagnosed clinically as having CS at the age of 5 years. He began riding a bicycle at 5 years. Chronic complications of CS observed include tremors, hypertonia, decreased lacrimation, and cutaneous photosensitivity.
Physical examination findings revealed hypertonia and hyperreflexia, head titubations, severe resting and intention tremors, dystonia, dysdiadochokinesia, and a wide-based ataxic gait. Further clinical details are given in Table 1. Neuroimages are presented in Figure 3.

Mutation analysis demonstrated 2 compound heterozygous CSA point mutations: c.479C>T (p.A160V), a missense mutation inherited from the mother that was previously reported in another patient; and c.1052G>A (p.S351N), a novel missense mutation inherited from the father (Figure 1C and D). Neither mutation was found in the control samples.

His tremors caused significant difficulty writing, feeding, and dressing. A trial of clonazepam did not result in an improvement in the tremors. He was prescribed a combination of carbidopa, 25 mg, and levodopa, 100 mg, and took half a tablet each morning, which improved his tremors; the resting tremor improved more than the intention tremor. The dose was gradually increased, and after 8 months he was taking 1 full tablet twice a day. His handwriting has improved, and he can color much more accurately than before. He has better endurance with activities such as walking, swimming, and riding a bicycle.

PATIENT 3

A 14-year-old girl with developmental delays was at her baseline until 2 years before presentation, when she developed motor difficulties. She was no longer able to climb a rope ladder or ride a pony. She developed gait difficulties, falls, tremors, choking and gagging on food, difficulty buttoning and zipping clothes, difficulty tying shoelaces, and problems navigating stairs. Her birth history was notable for the ultrasonographic finding of dilated cerebral ventricles and tube feedings in the first week of life.

Physical examination findings revealed a beaked nose and bilateral hand weakness. Tendon stretch reflexes were normal in the upper extremities, increased at the patellae, and absent at the ankles, with extensor plantar responses. She had fluctuating rigidity in the upper extremities, especially at the elbows, but without contractures. Dystonia and dysdiadochokinesia were present. She had a mild coarse postural tremor bilaterally and a shuffling gait with bradykinesia. Further details are given in Table 1. Nerve conduction studies demonstrated a mild sensory polyneuropathy (Table 2), and the results of needle electromyography of the right leg were normal.

Mutation analysis demonstrated 1 novel heterozygous missense mutation in CSA, c.3806A>C (p.D1269A), which was inherited from the asymptomatic father but was not observed in any of the control samples (Figure 1E). As yet, no other mutation in CSA has been identified in this patient. No mutations in CSA have been identified, but CSB protein was deficient in cultured skin fibroblasts (E.G.N., unpublished data, October 27, 2006). The results of genetic testing for GCH1 mutations were negative.

Therapy with a combination of carbidopa, 25 mg, and levodopa, 100 mg, was initiated at a half tablet twice a day. Three months later, her tremor had resolved, she used utensils more adroitly, she dressed herself better than before, and her movements were smoother. Her hypertonia had improved, and her steps were less shuffling. At 6 months, she continued to have clear improvements in multiple motor tasks with a significant beneficial effect on her daily life. At the 6-month visit, thyroid studies demonstrated mild hypothyroidism and thyroid supplementation was initiated. Nerve conduction studies demonstrated a sensory neuropathy, possibly related to the thyroiditis. Vitamin B12 and vitamin E levels were normal. Cerebrospinal fluid neurotransmitter metabolite, 5-methyltetrahydrofolate, neopterin, and biotin levels were essentially normal during a break from taking carbidopa-levodopa. Handwriting samples taken during and after this drug break illustrate the effect (Figure 2C and D).

We describe 3 adolescents with CS, all of whom had tremors and motor difficulties that responded to therapy with carbidopa-levodopa, with a significant beneficial effect on their daily activities and ability to care for themselves. These activities included tasks such as writing,
dressing, and eating and drinking. The parents of all 3 patients reported worsening of tremors and increased difficulty with motor tasks when doses of carbidopa-levodopa were unintentionally missed. This simple intervention has the potential to improve the quality of life significantly in affected individuals.

Our findings raise intriguing questions regarding the pathogenesis and therapy of CS. Delayed-onset progressive movement disorders have been observed in the setting of static acquired brain lesions, such as perinatal injury, stroke, and head trauma. Further localization is suggested by a comparison of the neuropathologic features of CS with those of Parkinson disease. In Parkinson disease, degeneration of the substantia nigra occurs, which provides dopaminergic input to the putamen. Calcification of the putamen is a hallmark of CS, with lesser degrees of calcification in the caudate, globus pallidus, and thalamus. In addition, the expression of glutamate transporters appears to be altered in the globus pallidus. Neuropathologic studies generally suggest preservation of the substantia nigra; however, 1 report observed brown discoloration of the substantia nigra. These findings suggest that the dopaminergic pathway may be injured in CS. There is also 1 report of a patient with

Table 2. Nerve Conduction Data for Patient 3

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Latency, ms a</th>
<th>Amplitude b</th>
<th>Velocity, m/s</th>
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<tr>
<td>Right median sensory</td>
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<td>31.90</td>
<td>54.80</td>
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<td>Right superficial peroneal sensory</td>
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<td>No response</td>
<td>No response</td>
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<tr>
<td>Left sural sensory</td>
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<td>No response</td>
</tr>
<tr>
<td>Right common peroneal motor</td>
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</tr>
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<td>3.50</td>
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</tr>
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<td>Fibular head</td>
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<tr>
<td>Popliteal fossa</td>
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<td>42.10</td>
</tr>
<tr>
<td>Right tibial motor</td>
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<tr>
<td>Popliteal fossa</td>
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<td>46.10</td>
</tr>
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</table>

a Latency is peak for the sensory studies and onset for the motor studies.

b Amplitude is given in microvolts for the sensory studies and in millivolts for the motor studies.

Figure 3. Cranial computed tomographic scans, taken at the ages of 9 years (A) and 15 years (B); the scans demonstrate bilateral basal ganglia mineralization and diffuse brain atrophy. The basal ganglia mineralization remains stable during this interval, whereas the ex vacuo ventricular dilation becomes more prominent over time.
CS whose hyperkinetic movement disorder improved with deep brain stimulation of the ventral intermediate nucleus of the thalamus. Some of our patients’ physical findings suggest the presence of cerebellar dysfunction, but the significance of this is unclear in light of the pathologic findings and their response to levodopa-carbidopa.

The link between the pathologic findings in the basal ganglia and the NER pathway is not yet clear. Recent work suggests that endogenous DNA damage may contribute to the pathophysiologic features of NER disorders. It is possible that the deep nuclei of the basal ganglia are more vulnerable to endogenous DNA damage and preferentially degenerate in CS, thus causing the movement disorders observed in our patients. Because this intervention in CS has not previously been described, further studies are warranted.

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REFERENCES