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Clinical Observations

Treatment of Leukoencephalopathy With Calcifications and Cysts With Bevacizumab

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ABSTRACT

BACKGROUND: Leukoencephalopathy with calcifications and cysts is a rare, autosomal recessive cerebral microangiopathy that causes progressive white matter disease, calcifications, and cysts within the brain. It is typically associated with slowly progressive psychomotor regression, seizures, and movement disorders. Although leukoencephalopathy with calcifications and cysts affects only the central nervous system, it demonstrates remarkable neuropathologic and radiologic overlap with Coats plus, a disorder of small vessels of the brain, eyes, gastrointestinal tract, and bone. Coats disease without extraocular involvement, a genetically distinct disorder from Coats plus, is characterized by retinal telangiectasias and exudative retinopathy, accompanied by neovascularization. Inhibition of vascular endothelial growth factor (VEGF) signaling with the monoclonal anti-VEGF antibody bevacizumab can improve retinal edema and exudates in Coats disease. Given these observations, we reasoned that VEGF inhibition might also be effective in treating leukoencephalopathy with calcifications and cysts and Coats plus, neither of which has any known therapy. **METHODS:** We treated an 18-year-old man with leukoencephalopathy with calcifications and cysts using biweekly infusions of the VEGF inhibitor bevacizumab for more than one year and performed clinical examinations and brain imaging at three month intervals. **RESULTS:** After treatment for more than one year, the patient showed improved bradykinesia and range of motion, and brain magnetic resonance imaging demonstrated a marked reduction in cyst volume and white matter lesions. **CONCLUSIONS:** Further studies in a cohort of patients are warranted to investigate the efficacy of VEGF inhibition as a treatment for leukoencephalopathy with calcifications and cysts.

Keywords: cerebrovascular disease, developmental disorders, genetics, movement disorders, leukodystrophy

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Introduction

Among the many causes of progressive cerebral white matter disease is a group of disorders that affect the microvasculature of the brain and sometimes other organs. These diseases include Coats plus and leukoencephalopathy with calcifications and cysts (LCC), both of which cause white matter disease and cerebral calcifications.[1] These diseases are frequently associated with psychomotor regression, epilepsy, dystonia, and spastic quadriparesis. Although Coats plus is caused by mutations in the conserved telomere maintenance component CTC1,[2] the genetic basis of LCC was only recently discovered to be because of autosomal recessive mutations in the box C/D small nucleolar RNA SNORD118.[3] LCC is a rare disease, with unknown frequency, and more than 70 patients have been reported in two large studies (with some patients described in both studies).[1,4]

Coats plus and LCC share similar pathology and imaging findings of white matter disease, calcifications, and cysts, but the clinical phenotype of LCC is apparently restricted to the brain, whereas Coats plus can involve other organs, including the eyes, gastrointestinal tract, and bones.[5] Coats plus is named for its shared ocular pathology with Coats disease, which combines retinal telangiectasias with exudative retinopathy and retinal neovascularization. Coats disease and the related familial exudative vitreoretinopathies have been treated successfully with inhibitors of vascular endothelial growth factor (VEGF) such as bevacizumab, which reduce retinal edema and exudates.[6-9] LCC and Coats plus currently have no established therapies, but given the similar microvascular pathology of Coats disease, Coats plus and LCC, we considered that VEGF inhibition might be helpful in treating LCC. This report describes the treatment of a single patient with genetically confirmed LCC with bevacizumab over the course of one year and his clinical and radiographic response.

Patient Description

The patient was born at an estimated gestational age of 29 weeks, weighing 1.62 kg, after a pregnancy complicated by premature rupture of membranes. After six weeks in the intensive care unit, he was discharged home and at age 11 weeks he developed seizures, which were easily treated. Developmental milestones were delayed: he sat independently at age 11 months (uncorrected), walked at 21 months, and at five years of age his language was estimated to be at the level of a three-year old.

The first focal motor deficit noted was at age six years, when the patient was found to have left-sided weakness and left ankle dystonia. By age seven years he was becoming progressively bradykinetic; he began levodopa-carbidopa and experienced mild improvement. He began to have difficulty ambulating at age ten years, and by age 13 years, he was falling repeatedly and had worsening dysarthria. He had a single, nonconvulsive, seizure at age 14 years and started using a cane to walk at home and a wheelchair for longer distances. He underwent scoliosis surgery at age 15 years, at which time he was diagnosed with depression and anxiety and treated with escitalopram. Gabapentin and baclofen were initiated because of worsening muscle spasms, and he continued to show progressive spastic quadriparesis.

Brain magnetic resonance imaging (MRI) at age six years, his first recorded cranial imaging, revealed calcifications in both cerebral hemispheres, without cysts or white matter changes. By age 13 years, when he had worsening dysarthria and falls, MRI demonstrated bilateral calcifications and cysts, some with contrast enhancement, in the periventricular regions, basal ganglia, and thalami, along with increased T2/FLAIR (fluid-attenuated inversion recovery) signal changes in periventricular and subventricular white matter. Repeat brain MRI at age 18 years demonstrated further progression of his imaging abnormalities, with increased calcifications in the periventricular white matter, basal ganglia, thalami, and dentate nuclei, associated with cysts in both hemispheres and subcortical white matter, without mass effect, and extensive cerebral and cerebellar white matter FLAIR hyperintensity. These clinical and radiological features were consistent with a diagnosis of either Coats plus or LCC. Genetic testing was negative for mutations in *CTC1*, whilst he was found to be compound heterozygous for two rare variants in *SNORD118*, n.*5C>G and n.81G>A, discovered as part of a genetic study to identify the cause of LCC.[2] His similarly affected brother carried the same two variants, with each parent being heterozygous for a single mutation.

At age 18 years our patient began treatment with bevacizumab, 5 mg/kg biweekly. Before initiation of therapy, his neurological examination was notable for bradyphrenia and the ability to answer questions with single words, with increased latency. Cranial nerves were otherwise normal. He was not able to lift the right arm above his shoulder and had minimal abduction of the left arm, with bradykinesia and spasticity in both upper extremities. He exhibited spasticity in both legs, more pronounced on the left, and he required maximal assistance in moving from the floor to standing or from supine to sitting. He required assistance to stand from a chair and moderate assistance for ambulation, with dystonic posturing and crouching gait. After 14 weeks of treatment, he demonstrated less bradykinesia and a greater range of motion of the arms compared with prior examinations. After six months of treatment, he could lift both arms above his head. In addition, range of motion measurements showed improvement in the hamstrings, hip abductors, and ankle dorsiflexors (other muscles were not measured) compared with pretreatment measurements. He stood from a chair without assistance and required only moderate assistance to transition from floor to standing and supine to sitting. He continued to require moderate help with ambulation, but initiated steps more quickly than he had six months previously. The clinical improvements in range of motion and bradykinesia plateaued after six months of bevacizumab, but he showed none of the decline in mobility that he had experienced over the years preceding treatment.

A follow-up MRI after three months of treatment showed a slight interval decrease in the size of the cystic lesions, most notably in the right corona radiata (Figure, E-F versus A-B), reduced FLAIR hyperintensity within the left cerebellar hemisphere (Figure H versus E), and interval resolution of FLAIR abnormality within the left cerebral peduncle. MRI after six months of treatment showed a further decrease in white matter FLAIR hyperintensity, with a marked reduction in the size of several thin-walled cysts (Figure I, J) and unchanged multifocal calcifications (Figure I). Imaging demonstrated continued reduction of cysts and white matter abnormalities between six months and one year of treatment (Figure M-P).

Throughout the course of his infusions he experienced a single nosebleed that was easily controlled, and none of the thromboembolic, hemorrhagic, or gastrointestinal adverse effects that have been reported for bevacizumab. His complete blood counts, electrolytes, creatinine, transaminases, and urine protein were monitored every two weeks while he was undergoing infusions and showed no abnormalities. Treatment was not continued beyond one year, given the plateau in clinical response after six months of bevacizumab, and the patient has remained clinically stable since his last infusion. The patient's brother was considered for treatment, but he had previously experienced multiple episodes of gastrointestinal bleeding because of recurrent vomiting, and his parents felt that he would not tolerate the frequent travel required for regular infusions. Thus, he did not receive bevacizumab, and his symptoms continued to progress during the period of his brother's treatment.