



**THE CENTER FOR PARKINSON'S DISEASE  
AND OTHER MOVEMENT DISORDERS**  
at Columbia-Presbyterian Medical Center

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March 16, 2000

Padraic J. Grattan-Smith, MD  
The New Children's Hospital  
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Sydney, AUSTRALIA

**RE: Leanna Mills  
Bethany Mills**

Dear Dr. Grattan-Smith,

Dr. Stanley Fahn and I had the pleasure of meeting Leanna and Bethany Mills on March 16, 2000 at the Center for Parkinson's Disease and Other Movement Disorders, Columbia-Presbyterian Medical Center, accompanied by their father, sister, and caretakers. We will now discuss each child separately for our own records and clarification.

Leanna is a 5 year old girl and probably right handed although she has switched to the left hand in the past. She was born at 38 weeks by elective C-section because of cephalo-pelvic disproportion. Her parents are non-consanguineous, and the pregnancy and early development were normal. However, later development was delayed with walking occurring at 18 months and speech was always slow and slurred. She first developed dystonia at age 2 with abnormal posturing of her right arm and inturning of her right foot with some unsteadiness with walking. During this time, she also had episodes of whole body tremors, brief 3-4 second episodes of being "spaced out", and had worsening of her speech. In October 1997, she had a RLL pneumonia and was admitted to the ICU. Following this illness, she developed worsening of her dystonia which spread to her left side and resulted in inability to walk. She also regressed developmentally and was no longer able to dress herself or use the toilet. She was treated with levodopa for approximately 4 months with an initial improvement which subsequently waned. Since then, she has been treated with Baclofen and has had a significant improvement in her dystonia, enabling

her to walk without assistance and has ability to perform some activities of daily living such as dressing herself. She presently attends pre-school but has been not progressing enough to continue on to kindergarten. In addition to the above problems, she is noted to have growth delay with a delayed bone age and low TSH and T3 levels. Recently, she has also had 3 episodes of vision loss lasting a few seconds and has worsening of her speech with decreased clarity and more "stuttering" over time.

Bethany was born at 39 weeks by elective Caesarian section without any complications with the pregnancy or early development. She walked at age 12 months and spoke her first words at 14 months. Dystonia was first noted in Bethany at age 2 1/2 in March 1999 following an episode of vomiting and diarrhea. Her right arm was twisted behind her back and she lost her ability to walk, although was still able to stand. She was treated with levodopa with only transient improvement. She apparently was still able to run in September 1999 but then in December she developed a viral illness with fever, and since then has only been able to crawl by putting her head to the floor and pushing herself on all four limbs. She has been treated with Baclofen 10 mg three times a day without significant improvement. She was recently given a trial of Artane but her father noticed increasing muscle jerks, so he discontinued it. She has also had some difficulties with her speech but it is unclear if there is also cognitive impairment. Of note, both girls seem to have a fluctuating course with worsening of dystonia occurring after any infectious illness.

Extensive investigations have been performed, mainly on Leanna, including multiple normal brain MRI's, normal blood count, biochemistry, calcium, magnesium, liver function tests, ammonia, serum lactate, copper, ceruloplasmin, ANA, chromosomes, lysosomal enzymes, carnitine and acyl carnitine, VLCFA's, transferrin isoforms, and CSF glucose and lactate. CSF neurotransmitter metabolites, tetrahydrobiopterin and neopterin were all normal. LM and EM of muscle, liver, skin and rectal biopsies were normal. The liver biopsy revealed the presence of pericanalicular whorled membranous material in occasional hepatocytes which probably represented a form of bile pigment but also may be present in early stages of Niemann-Pick disease, type C. Bone marrow, urine toxin screen, urine for organic acids and amino acids, and respiratory enzyme studies on liver and muscle were all normal. Fundoscopy was normal and there were no abnormalities of eye movements or KF rings. DYT-1 testing was negative in Leanna.

**Past Medical History:** Growth delay in Leanna with delayed bone age, low TSH and T3.

**Medications:** Baclofen 6 mg bid in Leanna, and 10 mg bid in Bethany.

**Family History:** There is no other family history of dystonia, tremor, seizures, or other movement disorders. They have an older sister with ADHD, and their father may also have attention deficit disorder.

**Review of Systems:** They both occasionally have poor appetite but no sleeping difficulties.

### **Physical Examination:**

**General Examination:** They were both generally in no apparent distress. There was a question of possible hypertelorism in both girls. Otherwise, there was not facial dysmorphism. There was no evidence of organomegaly or skin lesions.

### **Neurological Examination:**

They were both alert, playful, and fairly cooperative. Leanna's speech was very dysarthric and often difficult to comprehend. She was able to follow simple commands. Bethany also had slurring of her speech but not as severe as Leanna. Cranial nerves were intact in both girls with normal pupils, eye movements, symmetric facies, and midline tongue protrusion. Tone was decreased in all extremities. Coordination with finger to nose was intact for Leanna and she appeared to hold a pen normally without any abnormal posturing. Leanna was able to put her socks back on her feet. Coordination testing was limited in Bethany secondary to cooperation.

At rest, Leanna did not have any dystonia until she began to walk. With walking, she was noted to have a flexed posture of her right arm, inward turning of both feet, and a tilt of her trunk to the right. She was able to walk without assistance but had a tendency to veer to the right and bumped into the walls frequently. Bethany had dystonia apparent while sitting with deviation of her head to the right. She was only able to stand with one person assist, holding both of her hands. However, with this assistance she was able to jump up and down quite vigorously. She was unable to walk and crawled with anteroflexion and right torticollis, flexion of her trunk to the right, and dystonic posturing of her right arm. Reflexes were depressed in Leanna but 2+ in Bethany. Plantar response was flexor in both.

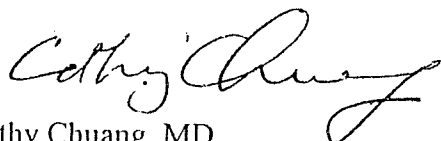
### **Impression/Plan:**

These are 2 sisters aged 5 and 3 with a history of generalized dystonia which began at age 2 in both girls. There is also associated dysarthria, possible learning disabilities, and growth retardation in the oldest child. Seizures may have also occurred in Leanna's early history. There has been an extensive evaluation without a definitive diagnosis. Examination in both girls revealed hypotonia, dysarthria, and generalized dystonia (greater on the right than the left, and more prominent in Bethany with only dystonia present with walking in Leanna). They have both had fluctuating courses with worsening occurring after infections, and transient responses to levodopa.

While at Columbia-Presbyterian, both girls were also evaluated by Dr. Darryl DeVivo from our division of pediatric neurology. His differential diagnosis includes Niemann Pick Type C, glutaric acidemia, type I, Schindler's disease, infantile neuroaxonal dystrophy, Hallervorden-Spatz disease, and mitochondrial disease. Blood was collected for screening of mitochondrial mutations. Skin biopsies were performed on both children to evaluate cultured fibroblasts for the enzyme deficiency in glutaric acidemia and Niemann-Pick Type C. Blood samples were also collected and sent to Dr. Laurie Ozelius at Massachusetts General Hospital in order to perform genetic testing for dystonia. This was coordinated by Dr. Susan Bressman at Beth Israel Hospital. We

would also recommend that Leanna and Bethany be seen by Dominic Thyagarajan (see address and phone number below) to assess for possible mitochondrial disease. If all these investigations are negative, these girls most likely have a primary idiopathic childhood dystonia. In reviewing the Australian family with whispering dystonia, we do not feel that these girls have any characteristics of this family.

Sincerely yours,



Cathy Chuang, MD  
Movement Disorders Fellow  
for Stanley Fahn, MD

I have reviewed and agree with the above history, examination, assessment, and plan.



Stanley Fahn, MD

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