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Stanley Fahn, M.D.  
NI-3

Re: Leanna Mills

B/D: 12/27/94

-and-

Re: Bethany Mills

B/D: 9/20/96

Appt: 3/16/00

Dear Stan:

I thank you and Cathy Chuang for asking me to see these two sisters from Australia. It is my opinion that they have a familial progressive syndrome with fluctuating dystonia and cognitive impairment. Despite many studies, the biomolecular basis for this familial syndrome remains unknown. I am confident that it is a biochemical defect underlying the symptomatic dystonia, and it is likely that the condition is transmitted as an autosomal recessive trait.

The family history appears to be noncontributory to the extent that I understand it. Only the father was present today with his three daughters. He was accompanied by two friends who were assisting him in the care of his daughters. His wife remains in Australia looking after their 8-month old daughter. Mr. and Mrs. Mills have four daughters. Katie, age 7 years is well although she has elements of inattentiveness and hyperactivity. Leanna, age 5 years and Bethany, age 3 years are affected by the dystonic syndrome, and Olivia, age 8 months, appears healthy in infancy and she is at home with her mother. The patients' mother is age 34 years. She is well as is her 32-year old brother. He has one boy and one girl - both healthy. A second brother died at age 28 years following an accident. He also had one son and one daughter who are healthy. The maternal grandparents are unrelated. The maternal grandmother is well - now age 57 years. The maternal grandfather died at age 54 years from a myocardial infarction. He also had chronic alcoholism. Mr. Mills is 38 years old and healthy as is his only sibling, a sister. She has two boys who are healthy. The paternal grandmother is 70 years old and of Italian descent. The paternal grandfather died at age 51 years from a problem associated with a heart valve.

Regarding Leanna: She now is 5 years old. Father reported no complications of pregnancy. The gestation lasted 38 hours. Labor was induced but failed to progress satisfactorily and culminated in a cesarean section. There were no complications and the newborn period seemed normal. Father could not recall any details but seemed to think that Leanna weighed around 4 ½ lbs. at birth.

Her early motor development appeared satisfactory although she was slightly delayed in several accomplishments. Father recalls head control and turning over at 12 months, crawling at 12 months, sitting alone at 14 months, standing alone and walking at 18 months. Her early behavioral and cognitive developments also appeared slightly slow. First words appeared at 18 months and phrases at 30 months. She was talking in complete sentences after age 3 years. Her speech and language skills are not adequate for her current age and father describes her as having mild cognitive impairments. Her coordination has always been poor. At age 3 years, she had an intercurrent viral illness. Within 24 hours, she had developed dystonic posturing of the right arm. Since that time, she has had recurrent neurological disturbances manifested principally by extrapyramidal symptomatology, motor difficulties and poor coordination. Recently, she has been treated with Baclofen and derives some benefit. She now is back on her feet although her movements are clumsy. Her cognitive impairment is evident and her language is delayed.

The physical findings today revealed an alert and friendly girl weighing approximately 10 kg. She was generally small in body proportions and her head circumference was 45.5 cm. I noted no other dysmorphic features or cutaneous abnormalities. She did have a prominent systolic murmur audible at the left sternal border and prominent cranial and cervical bruits. I noted no organ enlargement. She had a slightly droopy appearance to her upper eyelids. Otherwise, eye movements were full in all directions and pupils were equal and reactive. I noted no abnormalities of the ocular fundi. The lower cranial nerve functions were normal and specifically I noted no abnormalities of vision or hearing. There were no obvious sensory abnormalities. The limb and axial tone were decreased and a mild degree of spasticity was superimposed on the hypotonia. Her tendon reflexes were diminished throughout but she did have bilateral Babinski signs. Her stance was slightly broad based and her gait was mildly unsteady. There was only minimal evidence of limb dystonia when she was walking.

Regarding Bethany: She is now 3 years old. Like her sister, the pregnancy was 38 weeks in duration and uncomplicated. Labor was induced but delivery was accomplished by a cesarean section because of the failure of the labor to progress satisfactorily. There was no described fetal distress and the infant apparently appeared healthy at birth. She did have some difficulties sucking but otherwise was physically well. She weighed approximately 5 lbs. Her early motor development was better than her older sister's development. For example, father reports that she had head control and was turning over at 6 months, sitting alone and crawling at 7 months, standing alone unassisted at 8 months and walking unassisted at 12 months. He recalls that Bethany, at a younger age, could "run circles around her older sister". Now, Bethany is more disabled and non-ambulatory, and her older sister has recovered from a previous dystonic crisis.

Bethany's speech is inadequate for her current age. Speech and language developed slowly during the latter part of the second year of life. Until recently, she was able to talk in complete sentences. She is very incoordinated and currently is unable to ambulate independently.

At age 2 years, the parents were concerned because Bethany developed a right leg limp. This symptom resolved after 2 weeks. About 6 months later, she had an episode of gastroenteritis with diarrhea. The next day, she was totally disabled with generalized dystonia.

Bethany's examination today reveals a fair complexioned child who is larger than her older sister. She weighs approximately 11 ½ kg and the head circumference is 47.2 cm. I noted no dysmorphic features or cutaneous abnormalities. Her heart sounds were normal and her lungs were clear. There were no cranial or cervical bruits and there was no organ enlargement. Neurologically, she was alert and frequently laughed. Her eye movements were full although I had the impression that there was the slightest limitation of full up gaze. Pupils were equal and reactive and the ocular fundi were unremarkable. There were no abnormalities of vision or hearing and the lower cranial nerve function seemed to be intact. I noted no sensory abnormalities. She was generally incoordinated and largely remained lying on a grownup's lap or lying on the examining table. She was hypotonic at rest with dystonic posturing of the limbs. There was a minor asymmetry of the limb dystonia but it was otherwise generalized. The tendon reflexes generally were decreased. Occasionally, there was a brisk response when the tendon was tapped repeatedly. The right toe was clearly extensor and the left was equivocal.

In summary, these two sisters are clearly disabled by a chronic relapsing process that appears to be triggered by intercurrent infectious stress. The dominant clinical picture is that of symptomatic dystonia, but other systems are involved as well including pyramidal tract and cerebellum. Cognitive impairment and language delays also are shared by the sisters indicative of diffuse cerebral dysfunction.

Numerous studies have been performed and largely have been unremarkable. The DYT1 gene analysis on Leanna was negative. Neuroimaging studies have been uninformative. Analyses of blood, urine and CSF also have been normal including an analysis of CSF biogenic amines by Dr. Keith Hyland. Biopsies of several tissues also have been obtained including skin, muscle, liver, nerve and rectum. Very careful analyses of these tissues has been normal, militating against several disorders that should produce characteristic histopathological abnormalities.

The clinical presentation is quite consistent with an underlying biochemical defect that may be dormant under basal conditions. However, with infections or other possible stressors, the predisposition becomes obvious and the patients become clinically symptomatic. They experience partial recovery interictally, but the chronic course is one of slow regressive deterioration.

What are the diagnostic possibilities? It would appear that many disorders have been effectively ruled out. Certainly, the lysosomal disorders have been investigated and there is little or no support for these possibilities. Similarly, there is no laboratory evidence for a mitochondrial disorder and the various neuroaxonal dystrophies such as Hallervorden-Spatz disease and Schindler disease seem quite unlikely. The usual amino acidopathies and organic acidurias have been investigated and there is no laboratory evidence to support these possibilities.

I am always concerned about the possibility of glutaric aciduria type I until the enzyme, glutaryl-CoA dehydrogenase, has been assayed and found to be normal. Similarly, one can always hold out for additional evidence in support of a mitochondrial disturbance. If a mitochondrial disturbance were to exist in these two children, given the fact that the MRI scans, muscle biopsies and CSF analyses have been negative, I would suggest a mutation affecting complex I.

Are there other possibilities? Certainly so. For example, I would wonder whether triphosphate isomerase deficiency has been investigated. This condition can produce a progressive neurological disease that features extrapyramidal findings of a dystonic type. In addition, these patients may have tremor, cerebellar symptoms, pyramidal tract signs and evidence of spinal cord involvement. I was impressed that the tendon reflexes were disproportionately decreased in these children and Babinski signs were present. Triphosphate isomerase is an important enzyme in the glycolytic pathway. It may produce a multisystemic disease and the symptoms would include chronic hemolytic anemia, increased susceptibility to infections, cardiomyopathy and death in childhood. I found no laboratory reports regarding the hematological profiles of these children. The progressive neurological abnormalities generally appear in late infancy or early childhood.

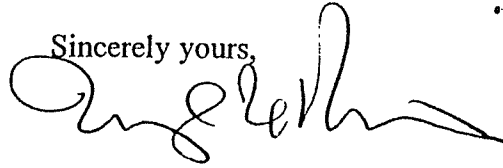
I did arrange with Dr. Michio Hirano to obtain skin biopsies on the girls so that we would have cultured skin fibroblasts for further study. As one example, triphosphate isomerase is deficient in all body tissues including cultured skin fibroblasts. The fibroblasts also would allow us to arrange for the assay of glutaryl CoA dehydrogenase and for various mitochondrial functions. Bloods also were obtained today for mitochondrial DNA mutational analyses.

Regarding treatment, I shall defer to you as it relates to the symptomatic dystonia. It appears that the children have benefited to some degree with Baclofen although other agents may be considered as well.

I thank you for referring Bethany and Leanna to me for an additional consultation.  
Please let me know if you have any further thoughts.

With thanks and best regards.

Sincerely yours,



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DCD/ahm

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