CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 14-2014: An 11-Month-Old Girl with Developmental Delay

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N Engl J Med 2014;370:1830-41.
DOI: 10.1056/NEJMcpc1305987

PRESENTATION OF CASE

Dr. Jenny Linnoila (Neurology): An 11-month-old girl was seen in the outpatient neurology clinic because of developmental delay.

The patient was born at another hospital by vaginal delivery after induction of labor at 38 weeks' gestation because of oligohydramnios. The mother had received prenatal care, including obstetrical ultrasonographic testing, the results of which were reportedly normal. Serologic screening tests during pregnancy were reportedly negative. The prenatal course was uncomplicated. The mother took ondansetron for nausea and levothyroxine for hypothyroidism and reported that there had been less fetal movement in utero as compared with her previous pregnancy. No meconium was present at delivery. The birth weight was 3.0 kg (25th percentile), the length 48.3 cm (25th percentile), and the head circumference 32.5 cm (10th percentile); the 1-minute and 5-minute Apgar scores were both 9. The newborn was admitted to the neonatal nursery. The results of newborn auditory screening were reportedly normal. Tests performed at the New England Newborn Screening Program were negative. She was discharged home on the third day of life. She reportedly fed well and developed and grew normally. She smiled, laughed, and interacted socially, but she vocalized little. At approximately 4 months of age, the infant's parents noted that she startled in response to loud sounds. At 6 months of age, she began rolling over from her stomach to her back and vice versa, reaching out for objects, and sitting with assistance. Her length was 69.9 cm (96th percentile), her head circumference 43 cm (72nd percentile), and her weight 8.5 kg (89th percentile). By 9 months, she could grasp objects and feed herself; however, her pediatrician noted that she sat only in the tripod position (back bent slightly forward, and arms placed forward with the hands near the feet). Two months later, her parents reported that she sat only briefly and then flopped over and that she had stopped reaching for objects and feeding herself. At age 11.5 months, she was referred to the neurology outpatient clinic at this hospital.

The infant's parents reported that she often appeared tired and less alert than she had earlier in her life. She did not crawl or pull to stand. She consumed dairy-based infant formula and soft baby foods and had maintained expected trajectories on

the developmental curves for height, weight, and head circumference. She smiled, made good eye contact, and responded to her name. She drooled frequently and made occasional mouthing movements. She did not choke or have trouble swallowing, she did not have constipation, and she did not have activity suggestive of seizures. She had had an ear infection at 4 months of age. Immunizations were current. She lived with her parents and her brother (3.5 years of age), who were well. Her mother was of Russian Jewish ancestry and her father of Irish and Italian ancestry. Her mother was gravida 4, para 2, spontaneous abortion 2. The family had traveled to the Caribbean and Italy. A paternal cousin had a mild speech problem; there were no other known neurologic conditions in the family.

On examination, the infant's facial features were nondysmorphic. The head circumference was 45 cm (50th percentile); the anterior fontanel was soft. Funduscopic examination was unsuccessful. There were two hypopigmented spots on her left thigh; examination with a Wood's lamp was negative, revealing no evidence of neurocutaneous lesions. There was no hepatosplenomegaly. On neurologic examination, she was subdued, appeared alert, and intermittently startled spontaneously. Pupillary reactions were normal, and ocular movements were full and conjugate, with horizontal and vertical eye movements that tracked the examiner's face, bright objects, and light, without saccadic intrusions or nystagmus. Movements of the infant's face and palate were symmetric. There were no tongue fasciculations or macroglossia. She smiled periodically, made brief chewing movements, puckered her lips, and drooled, but she did not vocalize. She turned her head to a bell ring. She opened her hands and moved her fingers. Her legs were extended tonically, with bilateral equinus foot posture (plantar flexion) and curled toes. When pulled to a standing position, she rose onto her toes. Muscle tone was increased, with rigidity; the heel cords were tight. The plantar reflexes were extensor; grasp and Moro reflexes were absent. A few unsustained beats of ankle clonus were present. In the prone position, she lifted her head briefly. Her head and neck drooped anteriorly when sitting. The asymmetric tonic neck reflex was incomplete. On testing of the parachute reflex (abduction of arms, extension of elbows and wrists, and spreading of fingers, elicited when an infant is held in suspension in the ventral position and is tilted abruptly forward toward the floor), she fisted both hands and did not spread her arms.

The blood level of aspartate aminotransferase was 159 U per liter (reference range, 9 to 80). Other test results, including blood levels of total protein, albumin, globulin, total and direct bilirubin, alkaline phosphatase, alanine aminotransferase, and creatine kinase, were normal, as were a complete panel of plasma amino acids and urinary levels of organic acids. An electroencephalogram showed the absence of sleep spindles during a relatively prolonged stage N2 sleep (a stage of non–rapid-eye-movement sleep characterized by sleep spindles), infrequent low-amplitude spikes in both centroparietal regions during sleep stage N2 (of uncertain clinical significance), and no electrographic or electroclinical features of seizures.

Dr. Otto Rapalino: Seven days after initial evaluation, magnetic resonance imaging (MRI) of the head was performed without the administration of gadolinium (Fig. 1). The image showed mild diffuse hypomyelination that was most conspicuous in the deep and subcortical supratentorial white matter, with relative sparing of the genu and splenium of the corpus callosum. T_2-weighted images of the posterior thalami and lentiform nuclei showed a subtle increase in signal. The anterior thalami appeared mildly hyperintense on T_1-weighted images and hypointense on T_2-weighted images. Single-voxel magnetic resonance spectroscopy (MRS) of the left frontal white matter revealed a slight decrease in the *N*-acetylaspartate-to-creatine ratio; the metabolite ratios were normal on MRS of the region of the left basal ganglia.

Dr. Linnoila: Additional diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Kalpathy S. Krishnamoorthy: I performed a neurologic evaluation of this infant when she was 11 months of age. Perinatal history was unremarkable, and there apparently had been no cause for concern during the first 6 months of life; concern about her development was raised when she was between 8 months and 11 months of age. She was nondysmorphic, with normal head growth. The motor examination was abnormal owing to increased muscle tone. Her vision

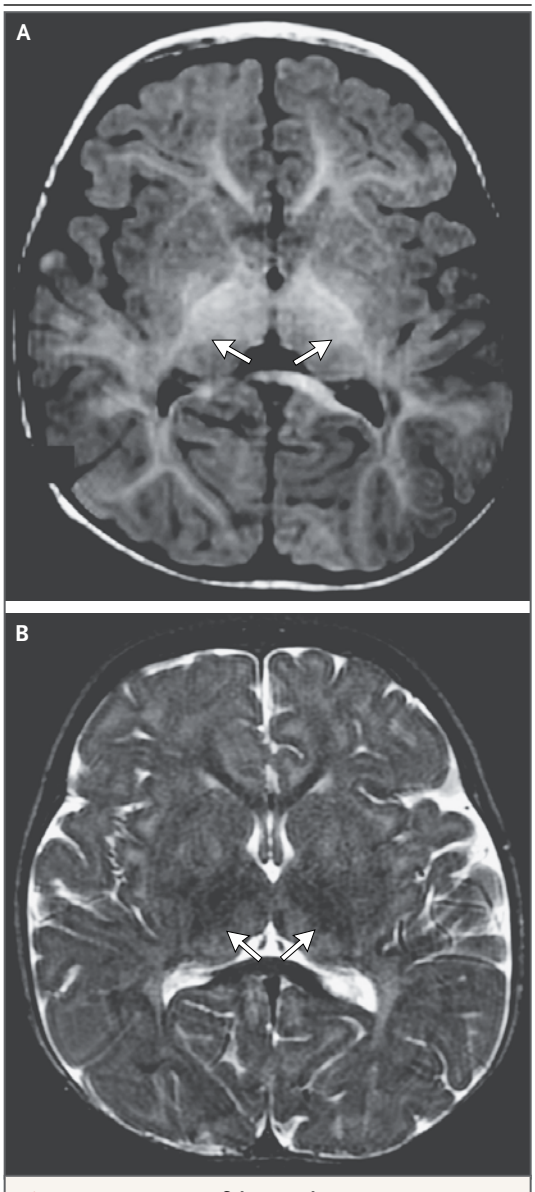

Figure 1. MRI Image of the Head.

Areas of subtly increased T_1-weighted signal (Panel A, arrows) and decreased T_2-weighted signal (Panel B, arrows) are evident in the anterior thalami. Mild, diffuse hypomyelination can be seen in the anterior limbs of the internal capsules.

appeared intact, but the fundi could not be evaluated. Developmentally, the patient had the skills of a 6-month-old infant. She had frequent startle responses, which were not of particular concern to the parents but were clinically relevant for the formulation of the diagnosis. We based the differential diagnosis on the clinical concerns and neurologic findings.

The first concern was the girl's developmental delay. Such a delay can be due to a nonprogressive (static) or a progressive (degenerative) neurologic disorder. In general, infants with nonprogressive disorders show signs of developmental delay but maintain their trajectory on the developmental curve; infants with progressive neurologic disorders reach a plateau and then lose their developmental skills. An overlap between progressive and nonprogressive neurologic disorders might make it difficult to distinguish between the two entities, and often the passage of time and careful follow-up evaluations are helpful. Developmental delay occurs in approximately 1 to 3% of children and can be isolated or global. A cause can be determined in 50 to 60% of cases; the most common causes of developmental delays are perinatal insults, chromosomal disorders, brain malformations, toxins, and autistic-spectrum disorders.[1,2] Metabolic disorders constitute only 1 to 3% of developmental delays.[3] At the time of this patient's initial presentation, it was not entirely clear whether her development was continuing its trajectory or had reached a plateau and started to regress.

The second concern was the infant's marked increase in muscle tone due to spasticity and rigidity. The Babinski sign was present bilaterally. These abnormalities localize to lesions in the motor pathways of the cerebral cortex, basal ganglia, central white matter, or brain stem and indicate bilateral corticospinal dysfunction. The significance of extensor plantar responses (Babinski sign) in newborns and young infants is an enigma. In clinical studies, 92 to 93% of healthy neonates had flexor plantar responses.[4,5] In general, extensor plantar responses in infancy should be interpreted in the context of other associated findings, such as asymmetry, hyperreflexia, and clonus.

NONPROGRESSIVE CAUSES OF DEVELOPMENTAL DELAY AND SPASTICITY

The first diagnostic consideration was whether the developmental delay and spasticity were due to a nonprogressive disorder, such as cerebral palsy, a controversial term that includes motor-impairment syndromes caused by lesions in the brain in the early stages of development.[6] The classification of spastic cerebral palsy, the common subtype, is made according to the topography of the lesions; the topography varies depending on whether the cause is spastic diplegia (e.g.,

cystic periventricular leukomalacia), spastic quadriplegia (e.g., hypoxic–ischemic injury), or spastic hemiplegia (e.g., perinatal stroke and malformations).[7] Causes of cerebral palsy are prenatal (60% of cases), perinatal (15 to 20%), or postnatal (10%).[6] Both chorioamnionitis and fetal thrombotic vasculopathy have been implicated as causes of cerebral palsy.[8,9] In one study, 70 to 90% of cases of cerebral palsy were associated with abnormal MRI scans.[7] In another study, predominant abnormalities associated with cerebral palsy included white-matter lesions on MRI in 43% of cases, although in 12% of cases, the MRI scans were normal.[10]

The practice parameters of the American Academy of Neurology recommend neuroimaging with MRI as the initial diagnostic test for evaluation of both cerebral palsy and global developmental delay.[11,12] Dr. Rapalino, would you discuss the differential diagnosis of the MRI findings?

Dr. Rapalino: The differential diagnosis of the MRI findings in the thalami includes inherited metabolic disorders, such as GM_1 or GM_2 gangliosidosis[13-15] and Krabbe's disease,[15] disorders caused by previous hypoxic–ischemic encephalopathy,[16] infectious processes (e.g., encephalitis associated with influenza A [H1N1] virus infection),[17] and encephalopathy caused by hypoglycemia.[16,18]

The MRI findings in the brain in patients with gangliosidosis include T_2-weighted hypointense and T_1-weighted hyperintense changes in the ventral thalami, increased T_2-weighted signal in the nuclei in the basal ganglia, and white-matter hypomyelination.[15,19,20] The infantile forms of GM_1 and GM_2 gangliosidoses are very difficult to differentiate on the basis of the findings on MRI. Infants with Krabbe's disease may have changes on MRI that are similar to the changes seen in infants with GM_1 or GM_2 gangliosidosis, but in cases of Krabbe's disease, the thalami and basal ganglia are less involved and the corpus callosum is frequently affected.[15] Although in this patient the findings in the deep gray matter on MRI might be caused by previous hypoxic–ischemic encephalopathy, viral encephalitis, or hypoglycemic encephalopathy, the clinical presentation argues against these causes.

Dr. Krishnamoorthy: This patient's normal early development and the findings on MRI did not favor a static disorder such as cerebral palsy. A number of genetic and neurometabolic disorders can mimic cerebral palsy (Table 1),[21] but this patient did not have the typical features of these disorders and thus including them in the differential diagnosis was not warranted.

Table 1. Metabolic and Genetic Disorders that Mimic Cerebral Palsy.

Glutaric aciduria type I
Lesch–Nyhan syndrome
3-Methylglutaconicaciduria
Pyruvate dehydrogenase deficiency
Pyruvate carboxylase deficiency
Cytochrome-c oxidase deficiency
Arginase deficiency
Ornithine transcarbamylase deficiency
HHH syndrome (hyperornithinemia, hyperammonemia, and homocitrullinuria)
Succinic semialdehyde dehydrogenase deficiency
Creatine transporter defect
Sulfite oxidase deficiency
Molybdenum cofactor deficiency
Dopa-responsive dystonia
Infantile neuroaxonal dystrophy
Hereditary spastic paraplegia
Ataxia–telangiectasia
Friedreich's ataxia

METABOLIC AND DEGENERATIVE DISORDERS

The second diagnostic consideration was whether the patient had a metabolic or degenerative disorder, with devastating consequences to her developing brain. Clinical suspicion for such disorders is often heralded by red flags, such as failure to thrive, intermittent encephalopathy, loss of normal milestones, consanguinity, seizures, movement disorders, vision or hearing impairment, excessive irritability or startle response, cognitive decline, and development of spasticity, some of which were noted in this patient. Clinical recognition of these disorders may be aided by physical findings on examination (Table 2).[22] Age at the onset of various metabolic and degenerative disorders differs. Most amino acid and organic acid disorders, urea-cycle disorders, and peroxisomal disorders are manifested in the neonatal period. Disorders that become apparent in early and late infancy include lysosomal storage disorders (e.g., Tay–Sachs disease, Krabbe's disease, Canavan's

Table 2. Clinical Clues to Possible Neurometabolic Disorders.*

Variable	Abnormality	Neurometabolic Disorder
Hair	Kinky hair	Menkes disease
	Thin or fragile hair	Hartnup's disease
	Alopecia	Argininosuccinic aciduria Biotinidase deficiency Hypothyroidism
Skin	Eczema	Phenylketonuria
	Photosensitive dermatitis	Hartnup's disease
	Blotchy macular eruptions	Homocystinuria
	Ichthyosis	Refsum's disease
	Angiokeratomas	Fabry's disease
	Dry skin	Hypothyroidism
Odor	Urinary musty odor	Phenylketonuria
	Urinary odor of maple syrup	Maple syrup urine disease
	Body odor of sweaty perspiration	Isovaleric acidemia
	Urinary or body odor of boiled cabbage	Hypermethioninemia
	Urinary odor of cat urine	3-Methylcrotonylglycinuria
Eye		
Lens	Cataract	Galactosemia Lowe's syndrome Fabry's disease
	Dislocation	Sulfite oxidase deficiency Molybdenum cofactor deficiency Homocystinuria
Cornea	Clouding	Hurler's syndrome (mucopolysaccharidoses) Mucolipidosis type IV Fucosidosis
Conjunctiva	Telangiectasia	Ataxia telangiectasia
Retina	Cherry-red spot	Tay–Sachs disease Sandhoff's disease GM_1 gangliosidoses Niemann–Pick disease Gaucher's disease Sialidosis type I
	Pigmentary retinopathy	Refsum's disease Zellweger's syndrome spectrum disorders Hunter's syndrome Pantothenate kinase–associated degeneration disease Cockayne's syndrome Farber's disease Lafora-body disease Neuronal ceroid lipofuscinosis Mitochondrial disorders Acanthocytosis

Table 2. (Continued.)

Variable	Abnormality	Neurometabolic Disorder
Optic nerve	Atrophy	Krabbe's disease
		Metachromatic leukodystrophy
		Canavan's disease
		Pelizaeus–Merzbacher disease
		Peroxisomal disorders
Face	Dysmorphic facial features	Mucopolysaccharidoses
		GM_1 gangliosidosis
		Inclusion-cell disease (mucolipidosis type II)
		Sialidosis (mucolipidosis type I)
		Fucosidosis
		Congenital glycosylation disorders
		Glutaric aciduria type II
		Cockayne's syndrome
		Hypothyroidism
		Peroxisomal disorders
Head	Macrocephaly	Canavan's disease
		Alexander's disease
		Megalencephalic leukoencephalopathy
		Glutaric aciduria type I
		D-2-hydroxyglutaric aciduria
		Hurler's syndrome
		Hunter's syndrome
		Tay–Sachs disease
	Microcephaly	Phenylketonuria
		Methylmalonic aciduria
		Citrullinemia
		Neuronal ceroid lipofuscinosis
		Congenital glycosylation disorders
		Succinic semialdehyde dehydrogenase deficiency
		Cholesterol biosynthesis disorder
		Serine synthesis disorder
		Sulfite oxidase deficiency
		Molybdenum cofactor deficiency
		Glucose transporter 1 deficiency
		Cerebral folate transport disorder
		Amish lethal microcephaly
Visceromegaly	Hepatosplenomegaly	GM_1 gangliosidosis
		Sandhoff's disease
		Gaucher's disease types 1 and 2
		Niemann–Pick disease
		Mucopolysaccharidoses
		Glycogen storage disease
		Inclusion-cell disease
		Galactosemia
		Mannosidosis
		Fucosidosis

Table 2. (Continued.)

Variable	Abnormality	Neurometabolic Disorder
Skeleton	Clinical and radiologic deformities	Mucopolysaccharidoses Gaucher's disease types 1 and 3 GM_1 gangliosidosis Mannosidosis Fucosidosis Inclusion-cell disease
Multisystem involvement		Mitochondrial disorders Lysosomal disorders Peroxisomal disorders Congenital disorders of glycosylation
Other	Family history of intellectual disability or cerebral palsy	High risk of neurometabolic disorders
	Consanguinity	High risk of neurometabolic disorders
	Excessive irritability	Krabbe's disease
	Early-onset severe epilepsy	Pyridoxine-dependency seizures Nonketotic hyperglycinemia Sulfite oxidase deficiency Molybdenum cofactor deficiency Folinic acid–responsive seizures Pyridoxal phosphate–responsive seizures Glucose transporter 1 deficiency Lysosomal disorders Peroxisomal disorders Organic aciduria and aminoaciduria Urea cycle disorders Biotin-responsive seizures Mitochondrial disorders Neuronal ceroid lipofuscinosis
	Intermittent encephalopathy	Aminoaciduria Organic aciduria Urea cycle disorders

* Some data are from Kolodny.[22]

disease, and metachromatic leukodystrophy), mitochondrial disorders (e.g., Leigh's disease), glucose transporter 1 (GLUT-1) deficiency, and congenital glycosylation disorders. This patient's normal early development, followed by developmental regression and the emergence of spasticity, led to a strong suspicion of lysosomal disorders. Clinical recognition of a lysosomal disorder may be facilitated by such features as dysmorphism, skeletal changes, and visceromegaly (Table 2); none of these findings were present in this patient. Retinal findings, such as cherry-red spots and optic atrophy, could also be diagnostic, but an eye examination after pupillary dilatation was not performed in this patient.

STARTLE RESPONSES

A unique feature of this patient's clinical presentation was frequent startle responses, which were exaggerated by sound stimuli. An exaggerated startle response in infancy is a characteristic feature of hyperekplexia (startle disease), but this patient's other clinical features were not typical of this disorder.[23] Myoclonic seizures may appear similar to startle responses in cases of myoclonic epilepsy, infantile spasms, childhood hypoxic brain injury, and a number of neurodegenerative disorders. Among the lysosomal disorders, a characteristic startle response occurs in infants with Tay–Sachs disease (GM_2 gangliosidosis or hexosaminidase A deficiency). In 1887, Bernard

Sachs wrote, "Hearing seemed to be very acute, there was unusual hyperexcitability to auditory and tactile impressions; the slightest touch and every sound were apt to startle the child."[24] Clinically, these startle responses appear spontaneously or as an extension response triggered by auditory stimuli (hyperacusis) and often begin before a patient is 4 months of age.[25] This patient's remarkable startle episodes were an affirmation and an important diagnostic clue for Tay–Sachs disease.

SUMMARY

In summary, I favored the diagnosis of Tay–Sachs disease because of the striking startle response in an infant with developmental regression and emerging spasticity. The diagnostic test was analysis of blood lysosomal enzymes.

DR. KRISHNAMOORTHY'S DIAGNOSIS

Lysosomal disorder; Tay–Sachs disease.

DIAGNOSTIC TESTING AND DISCUSSION OF MANAGEMENT

Dr. Florian Eichler: A lysosomal-enzyme screen, performed at the Lysosomal Diseases Testing Laboratory at Jefferson Medical College, in Philadelphia, revealed very low leukocyte hexosaminidase A activity (3.2%; normal range, >50.0%); other enzyme levels were within the normal range. This result is consistent with Tay–Sachs disease.

Genetic testing was performed at Baylor College of Medicine, in Houston, to confirm the diagnosis. This patient had one copy of a mutation in the hexosaminidase A gene (*HEXA*), which is commonly seen in infantile Tay–Sachs disease (c.1278insTATC), as well as a frameshift mutation in exon 11, which is the most common mutated allele seen in the Ashkenazi Jewish population. She also had one copy of a mutation that resulted in a premature stop codon (c.409C→T). Both mutations inactivate the enzyme and have previously been detected in patients with an infantile Tay–Sachs disease phenotype. Other mutations may allow for more enzyme activity and result in a milder phenotype.

Owing to the success of screening and the increase in intermarriage rates in the Jewish population, the disease is no longer consigned solely to the Jewish population. This patient, with her mixed ethnic background, reflects this trend.[26,27] The more diverse genetic admixture has decreased the sensitivity of DNA screening alone. In this family, screening had not been performed, but DNA screening alone would have given false reassurance concerning the father. Currently, enzymatic analysis is recommended as the primary screening method. DNA testing should be used to confirm results, identify cases of pseudodeficiency, and provide information for genetic counseling.

The lack of hexosaminidase A in persons with Tay–Sachs disease impairs degradation of the ganglioside GM_2, leading to excessive storage in neurons. In infancy, normal myelin development is also impaired. This leads to progressive weakness and loss of motor skills in the first year of life. Only one half of the patients learn to sit independently, and those that acquire this ability, such as this patient, lose it within 1 year. Early excessive startle was a pathognomonic sign. Once the diagnosis of Tay–Sachs disease was made in this case, pupillary dilatation to assess for a cherry-red spot was deferred.

The median survival among infants with Tay–Sachs disease is 47 months, and no treatment, including bone marrow transplantation, has been shown to favorably alter the natural history of the disease.[28] Symptomatic management with anticonvulsant and antispasmodic agents remains the mainstay of treatment. In this patient, muscle spasms and seizures developed over time, and sleep and respiratory difficulties worsened as the disease progressed.

We encountered enormous need for palliative care. Children with Tay–Sachs disease benefit from early access to palliative care specialists, as do children with other chronic life-threatening conditions.[29] The family decided not to have a gastric tube placed in the patient. Even with frequent home visits and hospice support, the patient's clinical course was protracted and, at times, painful for the family to witness.

The psychosocial needs of families with Tay–Sachs disease continue even after medical decision making has taken place. In this case, the suffering extended to parents, caregivers, and siblings alike. Of particular distress to the observers was the patient's excessive startle response, which is characteristic of this disorder. Even with attentive palliative care, effective overall management was challenging and often in-

complete, serving as a reminder that some symptoms have no easy remedies. The patient died at 28 months of age. An autopsy was performed.

PATHOLOGICAL DISCUSSION

Dr. Matthew P. Frosch: At the time of her death, the patient's weight was 8.2 kg (<5th percentile), and the height 87 cm (approximately 50th percentile). There was evidence of bacterial pneumonia in both lungs, with postmortem cultures growing both *Streptococcus pneumoniae* and *Haemophilus influenzae*. No other pathological changes were noted in the general autopsy findings.

The brain weighed 1238 g, which was slightly heavier than expected for the patient's age, and had a normal gyral pattern and a decreased volume of the cerebellum and the corpus callosum as compared with other regions. The brain was extremely firm in the fresh state, and this firmness persisted after fixation. In the fresh state, moderate abnormality was evident in the appearance of the cerebral cortex, which had a pinkish, hyperemic appearance; a portion of the white matter had a similar change in appearance (Fig. 2A and 2B). The overall organization of the brain, with cortical and subcortical structures, was normal.

Microscopic examination of the cerebral cortex and all other gray-matter regions showed that the neurons were markedly abnormal, with accumulation of large amounts of cytoplasmic material that stained intensely with Luxol fast blue (Fig. 2D). Markedly reactive astrocytes were intermixed with the neurons that were filled with storage material. In most brain regions, there was no evidence of similar storage material in the reactive astrocytes. A diffuse cortical gliosis was present, and some reactive astrocytes were in close apposition to engorged neurons (Fig. 2G).

Within the subcortical white matter, there was a marked loss of myelinated fibers, as well as an extremely brisk reactive astrocytosis. There was no evidence of perivascular accumulation of cells containing storage material, and there was minimal evidence of storage material in the cytoplasm of the reactive astrocytes.

On gross examination of the more posterior portions of the cerebral hemispheres, there was evidence of splitting of the cerebral cortex in the deeper layers (Fig. 2B). Microscopic examination of these regions showed pervasive neuronal accumulation of storage material. In the upper cortical layers, there was preservation of the overall texture of the neuropil, despite the neuronal distention and the reactive gliosis. In the deeper layers, however, there was neuronal dropout and the appearance of storage material, stained with Luxol fast blue, in the reactive astrocytes. This suggests that the more advanced lesions in the disease are associated with neuronal death and that, as a result, there is accumulation of the storage material in astrocytes.

The spinal cord was markedly involved by the process, with storage material in neurons of the dorsal horn, of Clarke's column, and of the anterior horn (Fig. 2F). There was marked pallor of the descending corticospinal tracts but relatively intact ascending fibers of the dorsal columns, suggesting that there was markedly less involvement of peripheral neurons (Fig. 2C). The cerebellum was markedly atrophic, with poor discrimination of gray and white matter on gross examination. Microscopically, there was neuronal accumulation of storage material in all the neuronal populations, including Purkinje cells, granule cells, and stellate cells. Accumulated material was also evident in the dendritic arbors of the Purkinje cells (Fig. 2E).

Electron microscopy of the cerebral cortex and other brain regions revealed that, despite the overall poor preservation of neuronal structure, there was evidence of storage material with numerous concentric membranous lamellar bodies (Fig. 2H). There was no evidence of similar storage material in either cardiac myocytes or hepatocytes.

Overall, the gross, microscopic, and ultrastructural findings in this case are consistent with a neuronal storage disease. Although the morphologic characteristics are not specific, they are fully consistent with the genetically determined diagnosis of GM_2 gangliosidosis (Tay–Sachs disease).

Dr. Nancy Lee Harris (Pathology): The patient's pediatrician is here today. Would you comment on your care of this patient?

Dr. Roger Spingarn (Pediatrics, Boston Children's Hospital and Newton–Wellesley Hospital, Newton, MA): This was an intensely difficult case for me as a pediatrician. Moving from the usual standard of helping a child overcome a disease to a palliative model required a leap uncommonly encountered in pediatrics. We are unaccustomed to helping a child die; here, we wanted to do so in a manner that provided dignity to the patient and honored the family's wishes. I think they

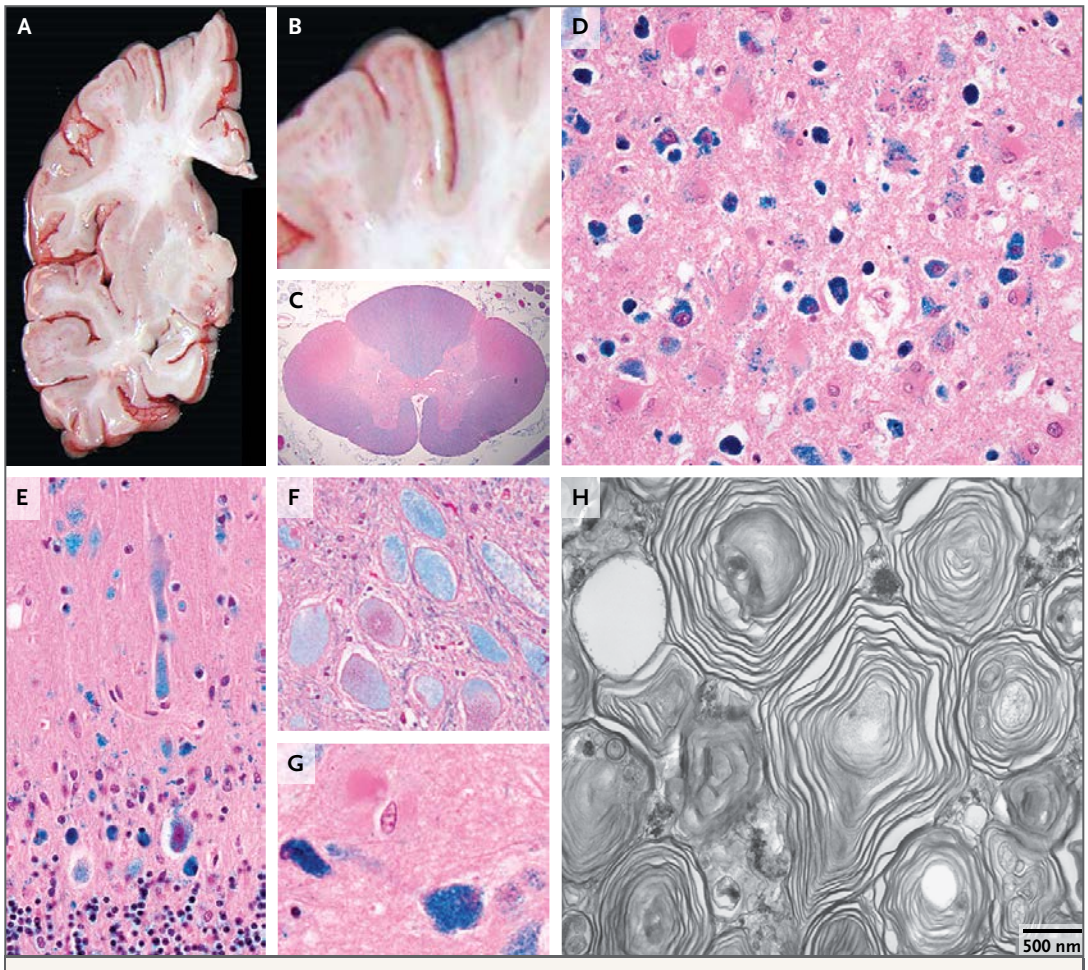

Figure 2. Pathological Findings at Autopsy.

A coronal slice of the brain (in the fresh state) at the level of the mammillary bodies (Panel A) shows a hyperemic appearance of the cerebral cortex. There is linear cavitation (Panel B) within the cortical ribbon. In the spinal cord (Panel C, hematoxylin and eosin and Luxol fast blue), there is marked pallor of the descending corticospinal tracts bilaterally. A specimen of the cerebral cortex (Panel D, hematoxylin and eosin and Luxol fast blue) shows the marked accumulation of material stained with Luxol fast blue in neurons, as well as reactive gliosis. A specimen of the cerebellar cortex (Panel E, hematoxylin and eosin and Luxol fast blue) shows the accumulation of material stained with Luxol fast blue in the dendritic arbor of Purkinje cells. A specimen of the spinal cord (Panel F, hematoxylin and eosin and Luxol fast blue) shows marked accumulation of material, positive on Luxol fast blue staining, in neurons of Clarke's column. A section of the cerebral cortex (Panel G, hematoxylin and eosin and Luxol fast blue) highlights the relationship between reactive astrocytes and neurons that contain storage material stained with Luxol fast blue. Electron-microscopic analysis (Panel H) shows that the accumulated matter in neurons corresponds to inclusions with concentrically organized lamellar membranes.

taught me more than I taught them. Caring for this lovely child and her family was a genuine honor. Care was provided during the patient's visits to her pediatrician's office and during home visits by a hospice physician, members of the hospital palliative care team, her neurologist, and her pediatrician. The patient never went to the emergency department and never needed in-patient care. The hospice physician was present daily or every other day during the final few weeks to help manage the patient's pain and autonomic storming (i.e., hypertension, dyspnea, intermittent agitation, dystonia, and disorientation).

Dr. Harris: Are there questions for our discussants?

Dr. Drucilla J. Roberts (Pathology): Was the placenta examined pathologically? Most such preg-

nancies will have some abnormalities, most commonly (in my experience) decreased fetal activity and mild fetal growth restriction, either of which should stimulate a pathological investigation of the placenta. Most lysosomal storage diseases have diagnostic placental pathological features, although in the case of Tay–Sachs disease, ultrastructural examination is required.[30,31]

Dr. Harris: We do not know whether the placenta was examined in this case.

Dr. Verne S. Caviness (Neurology): Is there a cell-biologic explanation for the early-onset startle response?

Dr. Krishnamoorthy: I posed this question to Dr. Edwin Kolodny, at New York University School of Medicine. He reported that in the 1970s, Dominick Purpura at Albert Einstein College of Medicine, in New York,[32] showed that infants with Tay–Sachs disease had meganeurite formation at the axon hillock of neurons that had been prepared with Golgi stain, a finding later confirmed by researchers at several other laboratories.[33] Along with this change was a remarkable increase in the number of spinous processes protruding from the axon at the same location as the enlargements. These spines are believed to be excitatory and can explain the remarkable startle response (Kolodny EH: personal communication).

ANATOMICAL DIAGNOSIS

Tay–Sachs disease (GM_2 gangliosidosis).

This case was presented at Neurology Grand Rounds.

Dr. Eichler reports receiving consulting fees from Shire/UBC and Alexion. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Thomas Byrne for assistance with organizing the conference and Dr. Roger Spingarn for assistance with the preparation of the case history.

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