Subdural Fluid Collections in Patients With Infantile Neuronal Ceroid Lipofuscinosis

Sondra W. Levin, MD; Eva H. Baker, MD, PhD; Andrea Gropman, MD; Zenaide Quezado, MD; Ning Miao, MD; Zhongjian Zhang, MD, PhD; Alice Jollands, MD; Matteo Di Capua, MD; Rafael Caruso, MD; Anil B. Mukherjee, MD, PhD

Objective: To describe subdural fluid collections on magnetic resonance imaging as part of the natural history of infantile neuronal ceroid lipofuscinosis.

Design: Case series.

Setting: Program on Developmental Endocrinology and Genetics, The Clinical Center, National Institutes of Health, Bethesda, Maryland.

Patients: Patients with infantile neuronal ceroid lipofuscinosis with subdural fluid collections.

Main Outcome Measure: Neurodegeneration on magnetic resonance imaging.

Results: During an ongoing bench-to-bedside clinical investigation, magnetic resonance imaging examinations led to the incidental discovery of subdural fluid collections in 4 of 9 patients with infantile neuronal ceroid lipofuscinosis. No particular event (such as trauma) or change in symptoms was linked to this finding, which was already in the chronic phase when discovered. Of the 4 patients, 1 was followed up for 7 years, 2 for 4 years, and 1 for 2.5 years. Over time, these collections remained stable or decreased in size.

Conclusion: Recognition that subdural fluid collections are part of the infantile neuronal ceroid lipofuscinosis disease process may obviate the necessity of additional workup as well as therapeutic interventions in these chronically sick children.

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Mutations in 8 different genes cause neuronal ceroid lipofuscinoses (NCLs), the most common (1 in 12,500 births) neurodegenerative storage disorders of childhood. The infantile form of NCL (infantile NCL [INCL]), the most lethal disease among all the NCLs, is caused by mutations in the palmitoyl-protein thioesterase-1 gene (PPT1). PPT1 catalyzes the cleavage of thioester linkages in S-acylated proteins, facilitating their recycling or degradation. The lack of thioesterase activity due to PPT1 mutation causes the accumulation of S-acylated proteins (ceroids), which leads to INCL pathogenesis. Children with this disease are normal at birth, but by 2 years of age they undergo complete retinal degeneration and by age 4 years brain activities become undetectable. Currently, there is no treatment for INCL and it remains a uniformly fatal disease. Our laboratory studies indicated that cysteamine bitartrate (hereafter cysteamine) and N-acetylcysteine facilitate the removal of ceroids from cultured cells in patients with INCL. A bench-to-bedside clinical protocol was initiated to determine whether cysteamine (Cystagon) alone or combined with N-acetylcysteine (Mucomyst) is beneficial for patients with INCL.

REPORT OF CASES

PROTOCOL

The clinical protocol was approved by the institutional review board of the Eunice Shriver Kennedy National Institute of Child Health and Human Development at the National Institutes of Health. To date, 9 patients with INCL (carrying the most lethal mutations in PPT1) were admitted to this protocol study and followed up for up to 7 years.

PATIENT 1

This patient entered the National Institutes of Health study at age 25 months. As
part of our ongoing evaluation, all patients in this protocol underwent head magnetic resonance imaging (MRI) examination, which included standard clinical images: T1-weighted, T2-weighted, fluid-attenuated inversion recovery, diffusion-weighted, and T2* gradient-echo images. Brain MRI of this patient at age 25 months demonstrated diffuse brain atrophy (Figure 1A). At age 31 months, extensive chronic subdural fluid collections, located adjacent to the frontal and occipital lobes, were discovered (Figure 1B); the occipital collections contained layering blood products. At age 34 months, surgical drainage of the fluid collections was performed at another institution. At age 38 months, brain MRI showed that the occipital fluid collections were slightly smaller, while the frontal fluid collections were similar in size and there were new blood products in the left frontal fluid collection (Figure 1C). During the next 5 years, these collections gradually became smaller, with evidence of further bleeding episodes in the left occipital collection between 63 and 74 months (Figure 1D) and again between 74 and 84 months (Figure 1E). Bridging vessels (Figure 1F), which are the likely source of the hemorrhages, as well as the simultaneous presence of subdural hemorrhages of varying ages (Figure 1G) can be readily visualized.

**PATIENTS 2 AND 3**

Patients 2 and 3 (fraternal twins) were enrolled in the protocol at age 27 months. During 4 years of follow-up, both patients demonstrated ongoing, albeit slow, developmental regression and progressive cortical atrophy. Serial T2-weighted images for patient 2 at ages 36, 45, 59, and 71 months show progression of the subdural fluid collection over time (Figure 2A-D). At 45 months, the brain MRI of patient 2 showed a small extradural fluid collection adjacent to the left frontal lobe and an even smaller collection adjacent to the right frontal lobe (Figure 2B). The collections showed evidence of blood products (Figure 2E and F). The subdural fluid collections became smaller during the following 2 years. For patient 3, bilateral parietal subdural collections were discovered at age 71 months (Figure 2G and H). Both collections contained blood products (Figure 2I and J).

**PATIENT 4**

Patient 4 entered the study at age 29 months. At this time, MRI showed progressive brain atrophy, and at age 49 months a follow-up brain MRI revealed subdural fluid collections adjacent to the left cerebral hemisphere (Figure 3A and B) and anterior to the tip of the right temporal lobe. Signals on the fluid-attenuated inversion recovery images (Figure 3C) suggested that blood breakdown products were probably present in the left hemisphere fluid collection, though hemosiderin was not detected. At age 58 months, follow-up brain MRI showed hemosiderin deposition in the right temporal fluid col-
lection (implying interval hemorrhage) and a significant decrease in the size of the left hemisphere fluid collection (Figure 3D). No traumatic events or abrupt changes in clinical status corresponding to the development of any of the fluid collections were noted in any of the 4 patients. No mass effect was noted for any of the fluid collections either.

**COMMENT**

The NCLs as a group are the most common (1 in 12,500 births) neurodegenerative storage disorders of childhood. Infantile NCL, caused by mutations in PPT1, is the most devastating form of this disease. The clinical symptoms of INCL include irritability, progressive visual loss leading to complete blindness, seizures, and psychomotor deterioration that finally progresses to a vegetative state followed by death. Pathologic findings include severe and progressive brain atrophy and the presence of autofluorescent storage material in both neuronal and other cell types. While the clinical manifestations of all types of NCLs are quite similar, the age at onset is variable. Thus, on the basis of age at onset, cellular ultrastructure, and the composition of the storage material, NCLs are classified into 4 major subtypes: infantile, late infantile, juvenile, and adult. Recent reports indicate that mutations of at least 8 different genes underlie the various forms of NCLs known to date.

During the course of an ongoing clinical study evaluating whether cysteamine and N-acetylcysteine are beneficial for patients with INCL, 4 of 9 patients were found to have subdural fluid collections. Previously, postmortem pathologic analysis of brains from patients with INCL have shown the presence of gelatinous subdural collections; these findings were correlated with MRI studies of patients with INCL. Moreover, the results of MRI studies in 18 patients with late infantile NCL, which is caused by mutations in the tripeptidyl peptidase-I gene (TPP1) and has a slower disease progression than INCL, have also been reported. However, subdural fluid collections in these patients were not specifically noted. Our results are consistent with those of earlier reports. Since 4 of 9 patients in our study had subdural fluid collections, we wondered whether cysteamine and N-acetylcysteine may have induced this abnormality. However, this possibility appears unlikely for the following reasons: (1) despite cysteamine having been used for many years in the treatment of cystinosis, subdural effusions have not been reported, and the only significant adverse effects of oral cysteamine use are gastrointestinal irritability and halitosis; (2) N-acetylcysteine also has a long history of safe and effective use as a mucolytic agent and in the management of acetaminophen toxicity as well as contrast-induced nephropathy, but subdural fluid collections have not been reported; and (3) subdural fluid collections have been observed previously during pathologic examinations of postmortem brains of untreated patients with INCL and in MRI studies, though the specific PPT1 mutations in these patients were not known; therefore, it could not have been ascertained whether these...
patients carried the lethal PPT1 mutations as in the current patient population.

Similar subdural fluid collections have also been reported in other progressive diseases with associated cerebral atrophy. For example, patients with Menkes syndrome, a neurodegenerative disorder of copper metabolism, also develop subdural fluid collections. In this syndrome, severe cortical and cerebellar atrophy are associated with abnormal cerebral vasculature, which may be one of the predisposing factors for the subdural fluid collections. However, marked cerebral atrophy and tearing of bridging veins as the brain recedes from the dura are also felt to account for this phenomenon. Subdural fluid collections as early as the neonatal period have been demonstrated on computed tomography in infantile olivopontocerebellar atrophy, a rare congenital disorder characterized by failure to thrive and neurological impairment. Glutaric aciduria type 1 is also a rare neurometabolic disorder that can present in the first years of life with chronic subdural hematomas that mimic nonaccidental trauma. Hermansky-Pudlak syndrome, manifested by oculocutaneous albinism, a storage pool deficiency, lysosomal accumulation of ceroid lipofuscin, and bleeding tendency, has also been associated with subdural fluid collections and retinal hemorrhages.

The prevailing theory of the formation of such subdural collections is the shearing of cortical veins, which become more vulnerable as cerebral atrophy progresses. Most of these disorders stand in stark contrast to reports of pediatric subdural hematomas occurring as a result of nonaccidental brain trauma. These patients often present with an acute onset of neurological symptoms. Additional supportive findings include retinal hemorrhages and occult fractures on radiological survey. Associated parenchymal injury may provide evidence for underlying traumatic brain injury. None of the patients with INCL in our study presented with acute neurological symptoms or changes in their neurological status, and MRI findings were coincidental. The recognition that subdural fluid collections in INCL develop as a consequence of the disease process may prevent unnecessary additional investigation and intervention in these chronically ill children.

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Correspondence: Anil B. Mukherjee, MD, PhD, The National Institutes of Health, Bldg 10, Room 9D42, 10 Center Dr, Bethesda, MD 20892-1830 (mukherja@exchange.nih.gov).

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Figure 3. Magnetic resonance imaging showing progression of subdural fluid collections in patient 4. The subdural collection appears between age 36 months (A) and 49 months (B) (arrows) and is less prominent at age 58 months (D) (arrows). C, A fluid-attenuated inversion recovery image at age 49 months shows that the fluid (arrows) does not have the same T1 as cerebrospinal fluid.