

Siblings With Cystic Leukoencephalopathy and Megalencephaly

ABSTRACT

Cystic leukoencephalopathy with megalencephaly is a newly described entity with mild clinical involvement. Patients suffer from developmental problems and seizures in childhood. Progression is gradual into adulthood. Typical magnetic resonance imaging findings include subcortical cysts and diffuse leukoencephalopathy. The etiology is unknown with possibly autosomal-recessive inheritance. We present two pairs of siblings with this disease and emphasize the characteristic and variable patterns even within the same family. (*J Child Neurol* 2000;15:690–693).

In 1995, van der Knaap and coworkers reported eight patients with a new leukodystrophy characterized by diffuse white-matter involvement with swelling and subcortical cysts.^{1,2} The cysts were in the anterior temporal and frontoparietal regions. The patients acquired macrocephaly during the first year of life and had relatively mild clinical problems. Some had seizures, developmental delay of varying degrees, and cerebellar signs; patients deteriorated slowly over the years with prominent ataxia and mild spasticity. Intellectual decline occurred in the second decade, although mental capacities remained relatively preserved even in adulthood. The mode of inheritance is possibly autosomal recessive. A metabolic or genetic defect has not yet been detected.

We present four patients from two families with this rare cystic leukoencephalopathy with megalencephaly to emphasize the inter-family variations of the magnetic resonance imaging (MRI), electroencephalographic (EEG), and clinical findings.

Case Reports

First Family (Figure 1). The first child, a 9-year-old boy, was noted to have macrocephaly in infancy. His head circumference was 36 cm at birth (75th percentile), 51.5 cm at age 9 months (4 cm above the 98th percentile), 53 cm at 12 months (4.5 cm above the 98th percentile), and 60 cm at 7 years (4 cm above the 98th percentile). His weight and height were in the 98th percentile at age 7 years. He walked at age 14 months and talked with simple sentences at 24 months. He had five tonic-clonic seizures precipitated by minor head trauma between the ages of 4 and 7 years. No seizures occurred while he was on valproate therapy. He attends primary school with declining performance in reading and arithmetic. Neurologic examination at age 7 years revealed mild mental retardation, cerebellar dysarthria, bilateral dysmetria, and dysdiadochokinesia. Cranial nerve and fundus examinations were normal. No pyramidal signs were present except for brisk reflexes. At 9 years of age, he developed prominent ataxia, walked with assistance, and had bilateral Babinski reflexes.

At 7 years of age, an EEG showed normal background activity. There were bilateral spikes and waves with double spikes over the parietal and temporal regions (right more than left) elicited by hyperventilation. Eye closure activated generalized discharges. During sleep, the epileptiform discharges shifted to the left frontal and right temporal regions with occasional generalization. Sleep spindles were not present. MRI at age 7 years showed symmetric diffuse involvement of the periventricular, lobar, and subcorti-

cal white matter with swelling, which led to flattened gyri. Cerebellar white matter and midbrain showed signal abnormalities without swelling. Multiple cysts were present in the subcortical white matter, most prominently in the left frontal and right temporal lobes, showing the same signal intensity as cerebrospinal fluid in all sequences. The internal, external, and extreme capsules, particularly the anterior limb of the internal capsule, were also involved. Corpus callosum, brain stem, basal ganglia, thalamus, and optic tracts were intact. In addition, a cavum septi pellucidi and cavum vergae were present.

The younger sister of the first patient was under observation. Macrocephaly developed early in infancy. Head circumference was 35.7 cm at age 9 days (60th percentile), 38.5 cm at 47 days (75th percentile), 41.4 cm at 80 days (98th percentile), 46.3 cm at 5 months (3 cm above the 98th percentile), and 53 cm at 15 months of age (5 cm above the 98th percentile). Motor development in infancy was uneventful. At age 2½ years, her neurologic examination and EEG were normal. Her MRI showed more pronounced swelling of the white matter (Figure 2) and larger cysts (Figure 3) than her brother had (Figure 4). The cerebellar and brainstem involvement was also more prominent, particularly in the dentate nuclei and tegmentum of the pons (Figure 5A and B). At age 3 years, she had seizures following minor head trauma. Brief language and motor regression followed these seizures. Her head circumference was 55.5 cm (4.5 cm above the 98th percentile). She became ataxic. A repeat EEG revealed occasional bioccipital sharp waves. Sleep spindles were present.

The patients' parents were first-degree relatives. Two first cousins of the patients had died with large heads, presumably as a result of uncontrolled seizures. The patients were born after uneventful pregnancies and deliveries. Their work-up included normal urinary *N*-acetyl aspartic acid, organic, and amino acid profiles; immunoglobulins; toxoplasmosis, rubello, cytomegalovirus, and herpes simplex titers; blood lactate and pyruvate levels; blood count; routine cerebrospinal fluid studies; and electromyography.

Second Family (Figure 6B). The first affected child sat at age 9 months, crawled at 14 months, and cruised at 24 months. At age 14 months, she started saying single words. At age 3 years, she became unable to cruise. Macrocephaly was noted at 2 years of age when she had seizures, which were initially febrile but became nonfebrile tonic-clonic seizures resistant to valproate and carbamazepine. At age 9 years, she was unable to walk, but sat unsupported. She was socially and verbally interactive, but was unable to attend school. Head circumference was 55.5 cm (3.5 cm above the 98th percentile) and there were bilateral cerebellar and pyramidal findings on examination.

An EEG at age 9 years revealed bifrontal beta activity that disappeared in deep sleep. There were bitemporal double-spike-and-wave discharges (right more than left) with occasional generalized spikes and

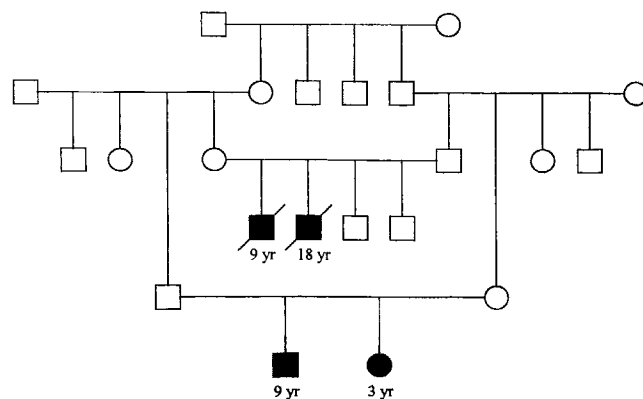


Figure 1. Pedigree of the first family. First cousins of the reported patients had died with large heads and seizures.

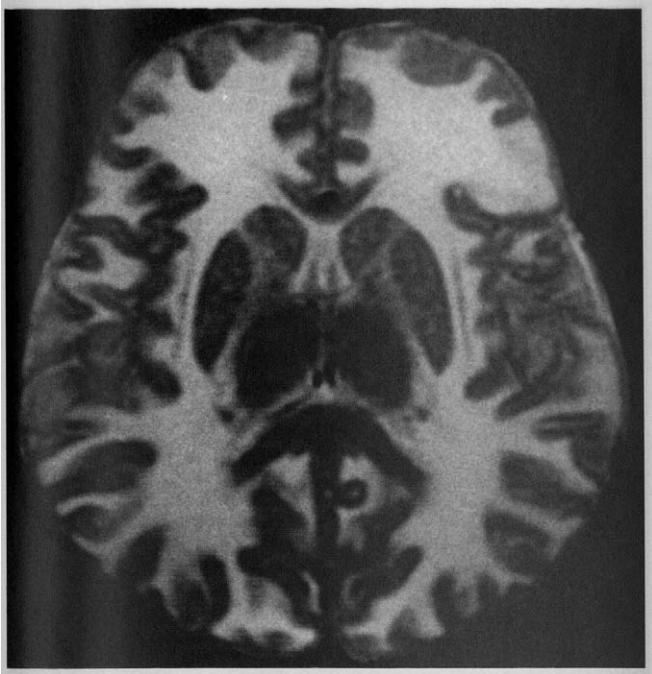


Figure 2. T_2 -weighted magnetic resonance image of the younger child of the first family. Note the diffuse white-matter involvement with flattened gyri.

waves. Sleep spindles were not present. Waking EEG showed normal background activity and generalized spikes and waves with eye closure, hyperventilation, and photic stimulation.

MRI at age 9 years showed diffusely swollen white matter with high T_2 signal. Cysts were present in the subcortical white matter, most promi-

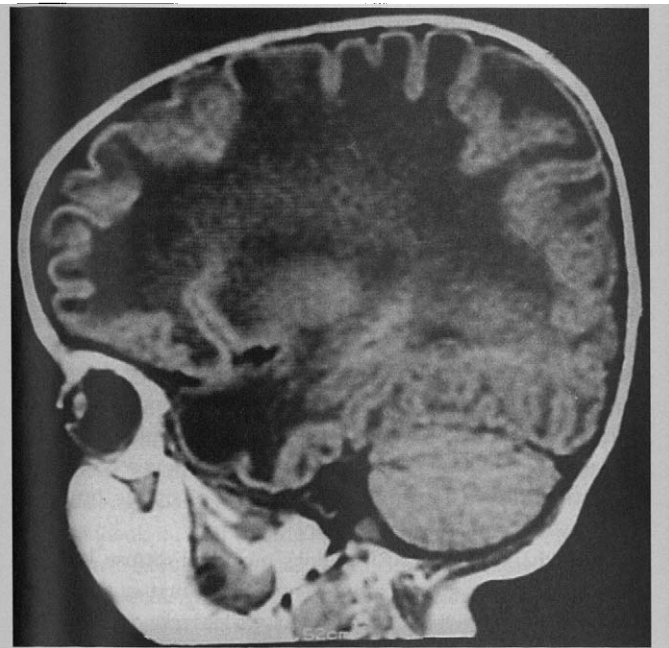


Figure 3. T_1 -weighted sagittal magnetic resonance image showing the large cyst at the pole of the temporal lobe of the younger child of the first family. The borders are barely visible because of the hypointensity of the surrounding area.



Figure 4. The older child of the first family. T_1 -weighted sagittal magnetic resonance image showing a small cyst at the pole of the temporal lobe.

nently in the temporal lobes. The remainder of the findings were similar to those of the first pair of patients, including the cavum septi pellucidi and cavum vergae (Figure 7).

The above patient's younger brother sat at 9 months of age, cruised at 24 months, and talked with single words. He was clumsy. Seizures occurred at 2½ years of age after minor head trauma. He continued to have partial-onset and secondarily generalizing seizures despite valproate and carbamazepine treatment. At age 7 years, he was unable to walk, but sat unsupported. He was interactive with limited cognitive function. His head circumference is 59.4 cm (6.5 cm above the 98th percentile). He also had cerebellar and pyramidal findings.

An EEG at age 7 years revealed bitemporal (right more than left) spikes and waves with occasional double spikes. Eye closure and photic stimulation at frequencies less than 15 Hz revealed activation with generalized discharges. Background activity and sleep organization were normal. His MRI was identical to his sister's.

The parents were fourth-degree consanguineous. Pregnancy and delivery were normal for both children. Their metabolic work-up included normal urinary organic acids and *N*-acetyl aspartic acid among the routine studies.

Discussion

The combination of leukodystrophy and macrocephaly is characteristic of both Canavan's disease and Alexander's disease, but they are also present in L-2-hydroxyglutaricaciduria, glutaricaciduria type 1, occasional cases of mucopolysaccharidosis, congenital muscular dystrophy, and GM₂-gangliosidosis. Most of these conditions lead to severe and progressive impairment. In comparison, patients with cystic leukoencephalopathy with megalencephaly have mild clinical problems despite striking involvement seen on imaging studies.

The etiology of cystic leukoencephalopathy with megalencephaly is unknown. Pathologic examination has revealed vacuo-

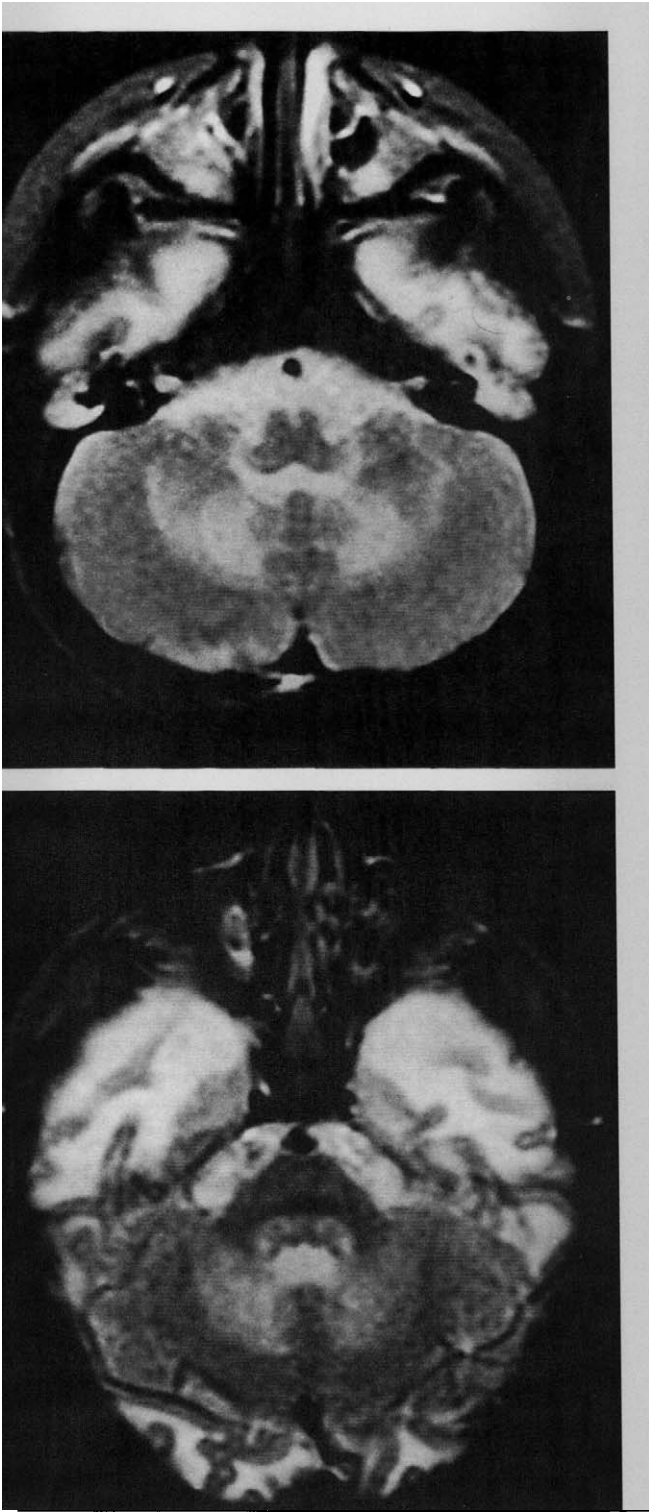


Figure 5. A, Hyperintense T₂ magnetic resonance signal around the dentate nuclei in the girl from the first family. Note less prominent involvement of the cerebellar white matter. B, Lighter involvement of the cerebellar white matter and hyperintensities of the pontine tegmentum seen on T₂-weighted images.

lating myelinopathy involving the outermost myelin lamellae.³ Magnetic resonance spectroscopy studies have not been conclusive for either neuronal or white-matter loss.¹ No metabolic abnor-

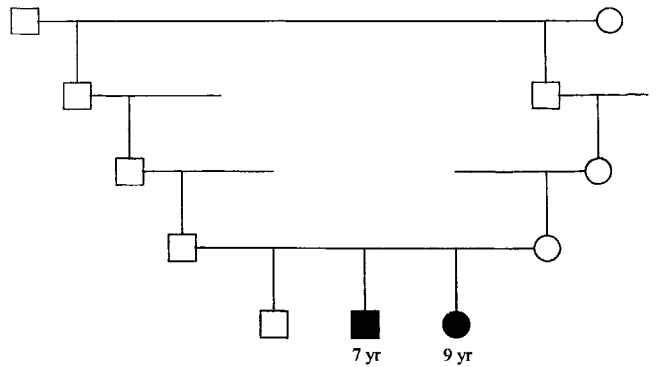


Figure 6. Pedigree of the second family. Consanguinity is fourth degree.

mality is demonstrated. There are many reported patients with cystic leukoencephalopathy with megalencephaly from Turkey and India⁴⁻⁶; however, cases are reported worldwide.⁷⁻¹⁰ Consanguinity appears to be a factor and the condition is seen in both girls and boys. Our report of these siblings also suggests a simple mendelian inheritance, possibly autosomal recessive. Investigations to identify the underlying genetic defect are in progress.

Megalencephaly develops early in infancy, as is clearly seen in our cases. The striking feature of cystic leukoencephalopathy with megalencephaly is mild motor and mental involvement despite severe imaging findings. Also evident in our cases are the cerebellar and pyramidal findings emerging after initially normal development. The second pair of patients has more severe involvement of motor functions: they are able only to sit. Although most patients remain ambulatory, the level of disability seen in our patients has been reported before.^{1,4} School attendance was not possible for the older child of the second family and impaired school performance was noted in the first family. Normal schooling has been reported rarely.⁶

Seizures precipitated by minor trauma are typical for cystic leukoencephalopathy with megalencephaly. Whether this represents a particular sensitivity to axonal injury in the brains of patients with cystic leukoencephalopathy with megalencephaly is unknown. The seizures are usually easily controlled with antiepileptic drugs, but our second family is an exception. The EEG findings are similar in our older patients: normal background activity and multifocal epileptiform discharges; generalized discharges are remarkable on eye closure. These prominent epileptiform findings are in contrast with those of the initial series.^{1,6} However, similar abnormalities have been reported in severely affected patients and in a possible early report of cystic leukoencephalopathy with megalencephaly.^{11,12}

The characteristic MRI findings include a diffuse leukoencephalopathy with sparing of the central white matter. Cerebellar white-matter and midbrain involvement are less pronounced. However, in our youngest patient (3 years of age) remarkable cerebellar dentate nuclear involvement is present; this has been reported before.⁷ The subcortical involvement gives a swollen appearance with flattening of the gyri. The swelling of the white matter is also

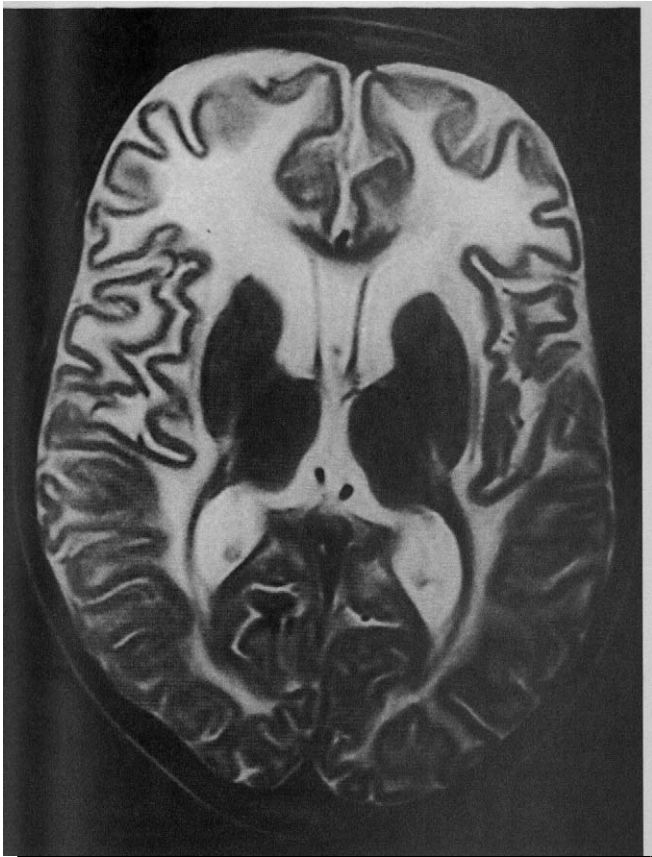


Figure 7. T₂-weighted magnetic resonance image of the 9-year-old child of the second family. Note the flattened gyri, especially of the frontal lobes, giving a swollen appearance. Optic tracts and corpus callosum are preserved. Internal capsule is partially involved.

more severe in the second sibling of the first family; this finding is known in younger patients.¹ The white-matter involvement in the second family is no different from that in the first family, but the clinical picture is more severe. Frontotemporal cysts are the other hallmark of this leukodystrophy. Our patients demonstrate all these findings. Although multiple and larger cysts are suggested to indicate the severity of the disease,¹² the younger sister in the first family has larger cysts but a good clinical status. In addition, the cysts in the second family are not greater in size or number, but the clinical state is significantly worse. On computed tomographic imaging, the cysts might not be evident. The subcortical cystic changes can also be seen in Alexander's disease, but frontal predominance, contrast enhancement, and the severe clinical involvement distinguish this entity.¹³

An identical MRI finding has been observed in a pair of normocephalic siblings evaluated in our clinic in adulthood with psychiatric problems, possibly representing a separate entity. Therefore, imaging features alone can be misleading, and clinical data are necessary for the correct diagnosis. However, there can be considerable variation in the degree of clinical or imaging involvement even within the same family. It is important to identify these patients correctly and counsel the families about the prognosis.

Cengiz Yalçinkaya, MD
 Department of Neurology
 Sinan Çomu, MD
 Pediatric Neurology
 Naci Koçer, MD
 Department of Radiology
 Adnan Yüksel, MD
 Department of Pediatrics
 Erem Gündüz, MD
 Veysi Demirbilek, MD
 Ayla Öcal, MD
 Departments of Neurology
 Cerrahpaşa Medical Faculty
 University of Istanbul
 Istanbul, Turkey

Received April 23, 1999. Received revised Sept 21, 1999. Accepted for publication Sept 22, 1999.

Address correspondence to Dr Cengiz Yalçinkaya, Department of Neurology, Cerrahpaşa Medical Faculty, University of Istanbul, Cerrahpaşa, Istanbul, Turkey. Tel: 90-212-6330176; fax: 90-212-6330176; e-mail: ycengiz@bistek.net.tr.

References

1. van der Knaap MS, Barth PG, Stroink H, et al: Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. *Ann Neurol* 1995;37:324-334.
2. van der Knaap MS, Valk J, Barth PG, et al: Leukoencephalopathy with swelling in children and adolescents. Magnetic resonance patterns and differential diagnosis. *Neuroradiology* 1995;37:679-686.
3. van der Knaap MS, Barth PG, Vrensen GFJM, Valk J: Histopathology of infantile-onset spongiform leukoencephalopathy with a discrepantly mild clinical course. *Acta Neuropathol* 1996;92:206-212.
4. Topcu M, Saatci I, Topcuoglu MA, et al: Megalencephaly and leukodystrophy with mild clinical course: A report on 12 new cases. *Brain Dev* 1998;20:142-153.
5. Yapici-Ucgul Z, Ucgul A, Deniz E, et al: Cystic leukoencephalopathies with megalencephaly in two siblings: Clinical characteristics, MRI and MRS findings. Poster abstract at the 8th International Child Neurology Association Congress, Ljubljana, Slovenia, September 13-17, 1998, *Brain Dev* 1998;20:376.
6. Singhal BS, Gursahani RD, Udani VP, Biniwale AA: Megalencephalic leukodystrophy in an Asian Indian ethnic group. *Pediatr Neurol* 1996;14:291-296.
7. Goutières F, Bouloche J, Bourgeois M, Aicardi J: Leukoencephalopathy, megalencephaly, and mild clinical course. A recently individualized familial leukodystrophy. Report on five new cases. *J Child Neurol* 1996; 11:439-444.
8. Koeda T, Takeshita K: Slowly progressive cystic leukoencephalopathy with megalencephaly in a Japanese boy. *Brain Dev* 1998;20:245-249.
9. Ben-Zeev B, Brand N, Prass E, et al: Megalencephaly leukodystrophy (van der Knaap syndrome) in 11 children of Jewish-Libyan and Turkish families: An opening for genetic linkage study. Poster abstract at the 8th International Child Neurology Association Congress, Ljubljana, Slovenia, September 13-17, 1998, *Brain Dev* 1998;20:359.
10. Cartwright JD, Gottlich E: Megalencephaly and leukoencephalopathy of infantile onset with mild clinical course. Poster abstract at the 8th International Child Neurology Association Congress, Ljubljana, Slovenia, September 13-17, 1998, *Brain Dev* 1998;20:360.
11. Harbord MG, Harden A, Harding B, et al: Megalencephaly with dysmyelination, spasticity, ataxia, seizures and distinctive neurophysiological findings in two siblings. *Neuropediatrics* 1990;21:164-168.
12. Mejaski-Bosnjak V, Besenski N, Brockmann K, et al: Cystic leukoencephalopathy in a megalencephalic child: Clinical and magnetic resonance imaging/magnetic resonance spectroscopy findings. *Pediatr Neurol* 1997;16:347-350.
13. Klein EA, Anzil AP: Prominent white matter cavitation in an infant with Alexander's disease. *Clin Neuropathol* 1994;13:31-38.