AJNR

Specific CT Findings in Krabbe Disease

Eddie Kwan, John Drace and Dieter Enzmann

AJNR Am J Neuroradiol 1984, 5 (4) 453-458
http://www.ajnr.org/content/5/4/453

Specific CT Findings in Krabbe Disease

Eddie Kwan[1, 2]
John Drace[1]
Dieter Enzmann[1]

Specific computed tomography (CT) findings in four patients with biochemically proven Krabbe disease included symmetric increased attenuation in the cerebellum, brainstem, thalami, caudate nuclei, and corona radiata before and in conjunction with decreased attenuation of white matter followed by atrophy at a later stage. Familiarity with the CT findings in the acute phase of Krabbe disease may assist clinicians in limiting the differential diagnosis and requesting appropriate laboratory tests.

Before computed tomography (CT), radiology had little application in the evaluation of neurodegenerative disease. However, CT has extended the dimensions of neuroradiology to include leukodystrophies, in which the predominant CT feature is a rather symmetric reduction in the attenuation of the white matter in the acute phase, followed by severe atrophy at a later stage. The sequence is characteristic for many leukodystrophies, but it is also nonspecific. Familiarity with the CT appearance of various leukodystrophies in the acute phase may guide the clinicians in limiting the differential diagnosis and obtaining appropriate laboratory tests. Despite the fact that there is no specific therapy for Krabbe disease or *globoid cell leukodystrophy*, a positive diagnosis is important for exclusion of other treatable disease, establishment of prognosis, and genetic counseling. In this report, four patients with biochemically proven Krabbe disease are described; three of them had CT findings that appeared to be specific for the acute phase of this disease. Such radiologic findings in an infant with progressive central nervous system and peripheral neuropathy strongly support the diagnosis.

Case Reports

Case 1

A 5-month-old boy was evaluated for irritability, hypotonia, and delayed motor milestones. Family medical history was negative, and pregnancy was unremarkable except for breech delivery. Beginning with the first week of life, his parents reported 20 to 30 prolonged episodes of high-pitched crying each day. He ate well, and height and weight developed normally. There was continual fisting of both hands, and he was unable to move either hand to midline after age 4 months. Screening for phenylketonuria, galactosemia, hypothyroidism, and TORCHS (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis) was negative. At 5 months, physical examination showed him to be attentive, with normal fixation but with marked irritability. There was profound hypoflexia and hypotonia. Cherry red spots and optic atrophy were not seen. Cerebrospinal fluid (CSF) protein was elevated to 149 mg/dl. Motor nerve conduction velocities were subnormal. Electromyography and muscle biopsy were unremarkable. Electroencephalography was minimally abnormal, with paroxysmal focal beta activity in the central vertex. Sural nerve biopsy was compatible with segmental demyelinization, but showed no metachromatic material. Leukocyte enzyme assays yielded beta-galactocerebrosidase activity of 0 U (normal range, 1.7–6.1 U); lactosylceramidase, 1.2 U (normal, 5.0–9.2 U); arylsulfatase-A, normal; and beta-galactosidase, 263 U (normal, 124–178 U).

This article appears in the July/August 1984 issue of *AJNR* and the September 1984 issue of *AJR*.

Received August 4, 1983; accepted after revision January 9, 1984.

[1] Department of Diagnostic Radiology, Stanford University School of Medicine, Stanford, CA 94305.

[2] Present address: Department of Radiology, Section of Neuroradiology, New England Medical Center, 171 Harrison Ave., Box 219, Boston, MA 02111. Address reprint requests to E. Kwan.

***AJNR* 5:453–458, July/August 1984**
0195-6108/84/0504-0453 $2.00

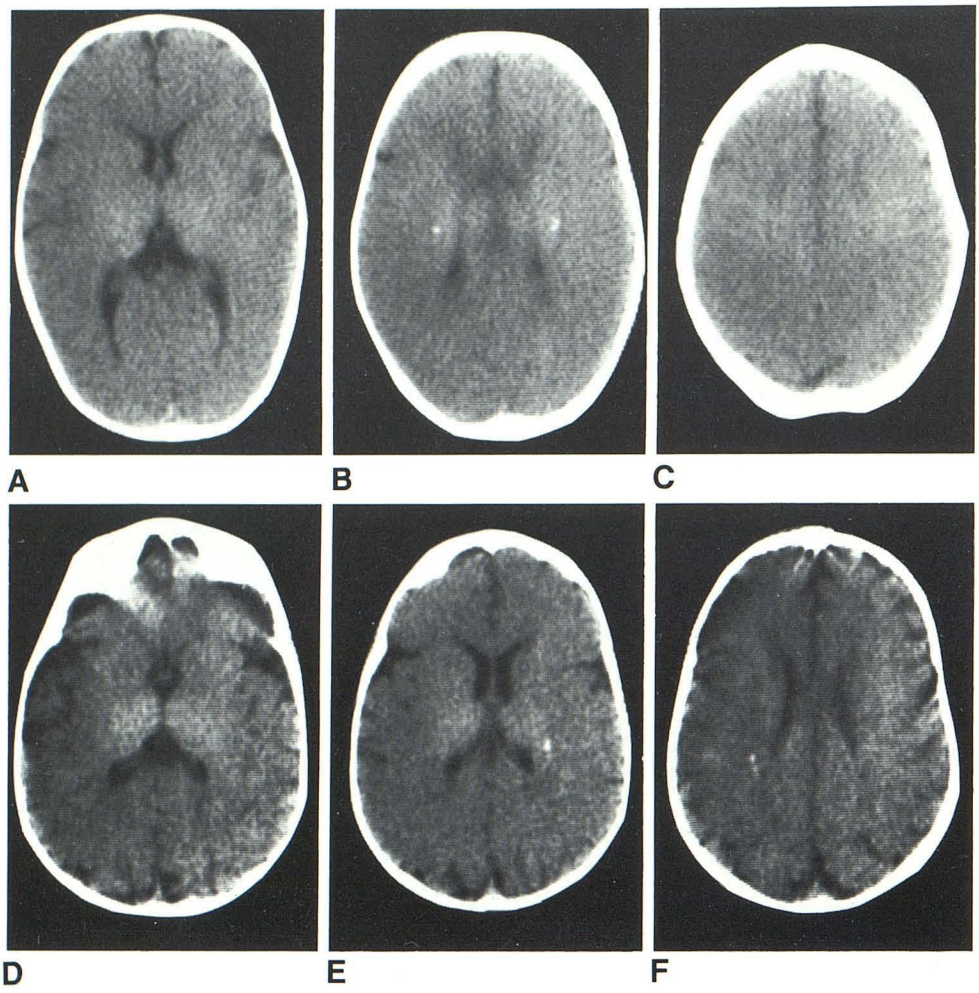


Fig. 1.—Case 1, 5-month-old boy with Krabbe disease. Nonenhanced CT scans. Symmetric increased density of thalami, body of caudate nuclei, and corona radiata (**A** and **B**). Symmetric punctate high density in corona radiata (**B**). Atrophy or demyelination not yet detected (**C**). **D–F**, 1 month later. Persistent increased density in thalami and new abnormal low attenuation along right corona radiata anteriorly (**F**).

Case 2

A 5-month-old girl was referred for evaluation of progressive quadriparesis, intractable irritability, and developmental delay. Family medical history and pregnancy were unremarkable. During the first 1–2 months of life, her parents noted persistent leg clonus, apparent lack of social interaction, and an abnormal sleep pattern. The infant ate well, and initially gained weight normally. At 3 months of age, she began a 10%–25% drop off from the growth curves in both length and weight. She never developed the ability to roll over or to bring her hands to midline. Physical examination showed an alert, but irritable and poorly responsive, infant. Her muscle bulk was normal, but there was marked hyporeflexia and increased extensor tone. Fundi showed optic pallor but no atrophy or evidence of storage disease. The electroencephalogram was normal. CSF protein was 150 mg/dl. TORCHS titers were negative, and screening for phenylketonuria, galactosemia, and hypothyroidism had been normal. Leukocyte enzyme assays showed normal beta-galactosidase and arylsulfatase-A activity, but extremely low beta-galactocerebrosidase (0.008 U) and lactosylceramidase (0.04 U) activities.

Case 3

This male infant was well until 6 months of age, when he developed gradual onset of loss of consciousness, hyperirritability, frequent high-pitched crying, and occasional seizure activity. At 1 year of age, he developed opisthotonos, absent reflexes, and optic atrophy. He was quiet and unresponsive most of the time. A CT brain scan was obtained at 1 year of age. Krabbe disease was confirmed by leukocyte enzyme assays.

Case 4

A 3-month-old girl was referred for evaluation of irritability, failure to thrive, developmental delay, and multiple episodes of choking while being fed. Family history was pertinent in that two of the patient's cousins died of metabolic neurologic disease before the age of 1 year. Our patient's clinical presentations and progressions were similar to her cousins'. CT brain scans, without and with contrast administration, were obtained at ages 3 and 5 months. Krabbe disease was again confirmed by leukocyte enzyme assays. There was no biochemical abnormality in calcium, phosphate, or iron metabolism.

Subjects and Methods

Cases 1 and 3 were scanned with the GE/CT 8800 scanner, using 10 mm collimation (320 × 320 matrix). Case 2 was scanned with the EMI Mark I head scanner, using 8 mm collimation (256 × 256 matrix).

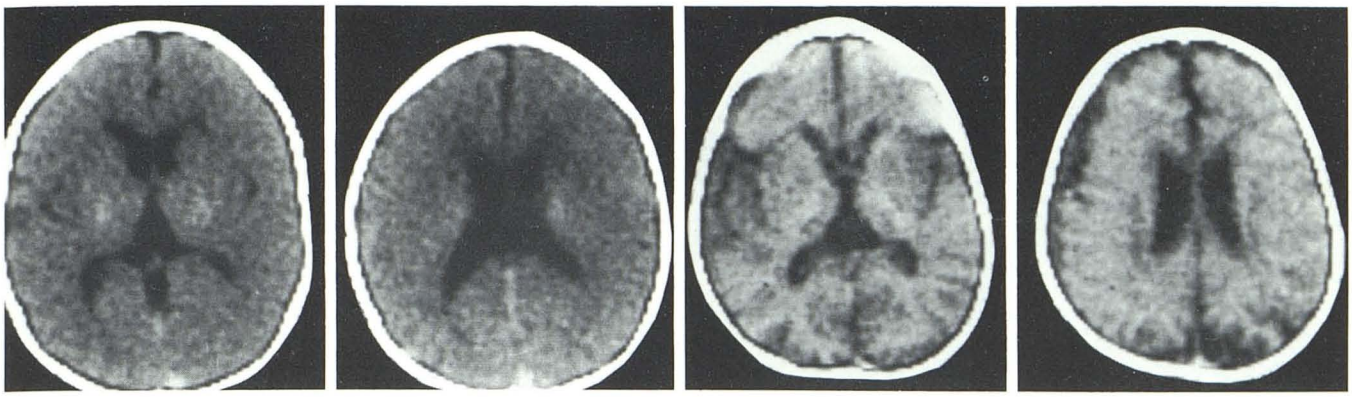
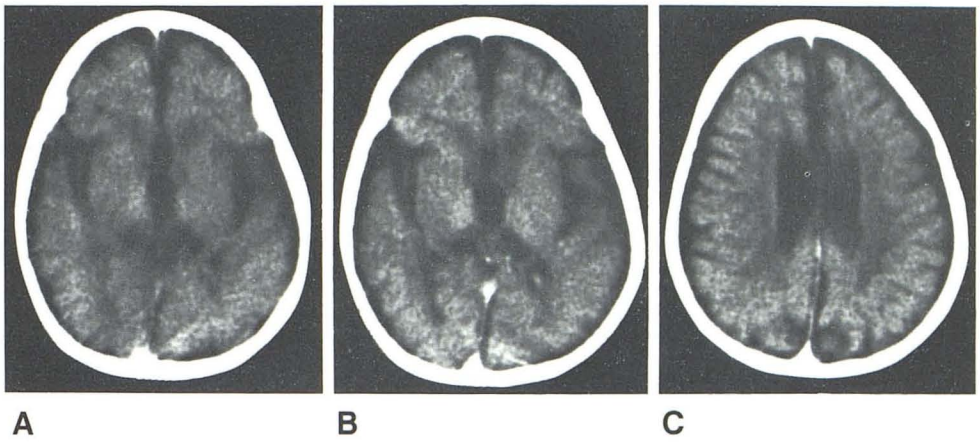


Fig. 2.—Case 2, 5-month-old girl with Krabbe disease. Nonenhanced scans. **A** and **B**, Symmetric increased density in thalami, body of caudate nuclei, and corona radiata. **C** and **D**, 6 months later. Rapidly progressive atrophy and symmetric abnormal low attenuation in corona radiata.

Fig. 3.—Case 3, 1-year-old boy with Krabbe disease. Nonenhanced scans. Symmetric increased attenuation in thalami (**A** and **B**), extensive periventricular demyelination, and atrophy (**C**).



Case 4 was scanned with the Siemens Somatom 2 scanner (256 × 256 matrix). Conray 60% was infused at 2.2 ml/kg of body weight in cases 1, 2, and 4.

Results

The striking finding in all four patients with Krabbe disease was the increased density of the thalami, caudate nuclei, and corona radiata before and in conjunction with the later findings of decreased attenuation in the white matter and atrophy. The increased density was noted early in the disease course: at 5 months of age for cases 1 and 2 (figs. 1 and 2); at 3 months of age for case 4 (fig. 4); and persisted into the latter stages, age 1 year, for case 3 (fig. 3). The difference in density between the thalamus and cortical gray matter was 10 H in case 1; this patient also had a unique finding of symmetric, punctate, extreme high density in the corona radiata (fig. 1B). On follow-up scans, the increased density in the thalami persisted as white-matter abnormalities, and atrophy appeared (figs. 1, 2, and 4). The difference in density, however, became less striking (figs. 2 and 3). In case 4, additional unique CT findings included generalized symmetric high density in the cerebellum with sparing of the dentate nuclei. There was patchy high density in the upper pons, midbrain, and subcortical white matter high up in the frontal convexity. The cerebellum, thalami, cortical gray matter, and subcortical white matter had readings of 39.8 H, 39.5 H, 33 H, and 28.9 H, respectively (fig. 4), thus establishing that the increased density was a real finding and not an optical illusion from diffuse decrease in the density of the surrounding white matter.

All four patients eventually exhibited atrophic changes. These developed rapidly over a 1-month period in case 1, over a 2-month period in case 4, and at 6 months in case 2. The white-matter low-density abnormalities were periventricular, somewhat asymmetric, and not particularly striking in their low density (figs. 1–3). There was no evidence of periventricular demyelination in case 4 on the latest scan at 5 months of age.

Discussion

Krabbe disease, or *globoid cell leukodystrophy*, is a rare, autosomal recessive, inherited degenerative disease of the central and peripheral nervous systems that results from

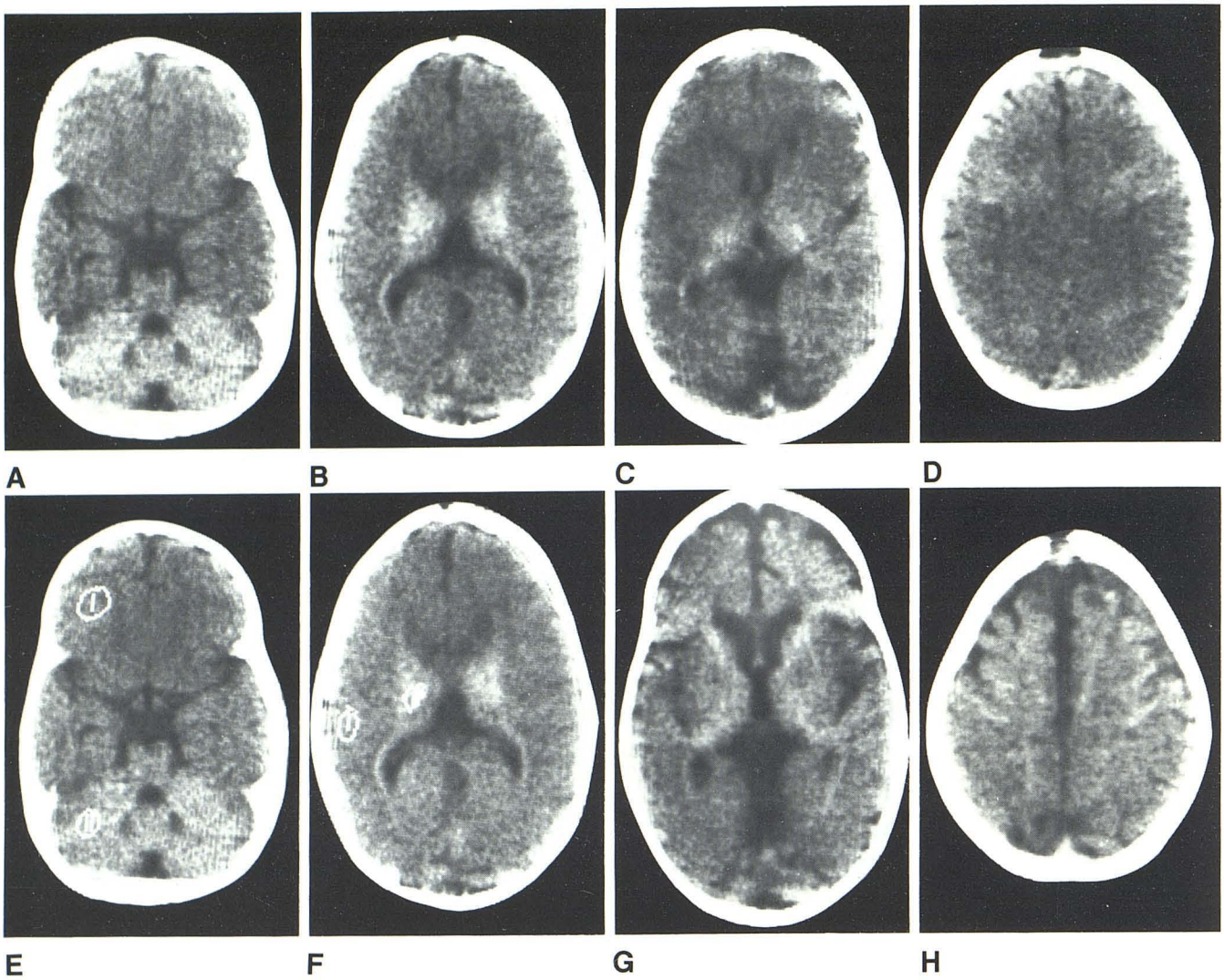


Fig. 4.—Case 4, 3-month-old girl with Krabbe disease. Nonenhanced scans. **A–D**, Symmetric increased attenuation in cerebellum (with sparing of the dentate nuclei), thalami, and body of caudate nuclei. Patchy asymmetric increased density in brainstem, corona radiata, and subcortical white matter. **E** and **F**, Hounsfield units of cerebellum (39.8 H), thalami (39.5 H), cortical gray matter (33 H), and subcortical white matter (28.9 H). **G** and **H**, 2 months later. Persistent increased density in cerebellum, thalami, caudate nuclei, and subcortical white matter; enlargement of cortical sulci and ventricular system signifies onset of atrophy.

almost complete deficiency of beta-galactocerebrosidase activity. The first report of globoid cell leukodystrophy was by Bullard and Southard in 1906, but, because of the clinical and neuropathologic description of five cases provided by Krabbe [1] in 1916, his name has been associated with it. Clinical signs and symptoms typically emerge at about 2–6 months of age, after which the affected infants rapidly lose previously attained developmental skills. These infants usually fail to thrive, have unexplained fever, irritability, myoclonic seizure, blindness, spasticity, and quadriparesis. They usually die within the first 2 years of life in a decerebrate state. More recently, the late infantile and juvenile form of Krabbe disease has been described in the neurologic literature [2]. The diagnosis is confirmed biochemically by low beta-galactocerebrosidase activity in the serum, leukocyte, cultured skin fibroblast, or amniotic cells. Supportive evidence is progressive slowing of peripheral nerve conduction velocity [3] and elevated CSF protein. There is biochemical evidence to suggest that the late-onset form of Krabbe disease has a slightly higher beta-galactocerebrosidase activity than the infantile form, and may represent a different allelic mutation of the beta-galactocerebrosidase locus.

Krabbe disease is characterized histologically by the severe loss of oligodendroglia and a profound degree of demyelination in the cerebral hemisphere, brainstem, cerebellum, and spinal cord. The very small amount of myelin that can be isolated from brains of such patients is normal. The reason for this is not entirely clear, but it has been postulated that the myelin present is formed during early myelination, before the enzyme deficiency is fully manifested biochemically [4]. Prominent glial cells, *globoid cells*, are thought to be modified macrophages containing galactocerebroside, which is a

breakdown product of myelin. Peripheral nerves also exhibit segmental demyelination.

The previously reported typical CT findings include a normal scan at an early stage, low attenuation in the periventricular white matter in the intermediate phase, and atrophy at the late stage [5–9]. Recently, a case of Krabbe disease was described showing white-matter rarification in the brainstem and cerebellar hemispheres (Lane B, personal communication). These sites of involvement were found to be a feature distinguishing Krabbe disease from other leukodystrophy. The typical sequence of radiologic findings in Krabbe disease is best explained in light of the known pathologic progression of the disease. The normal scan represents the early stage of Krabbe disease before the onset of extensive myelin breakdown and its attendant changes. Lower attenuation in the white matter during the intermediate stage signifies active demyelination associated with increased water content in the white matter, followed by atrophy at a later stage [5].

The new CT findings seen in all four of our patients are the symmetric increased densities in the thalami, corona radiata, and body of the caudate nuclei. In addition, case 4 demonstrated increased density in the cerebellum, brainstem, and subcortical white matter. To the best of our knowledge, these additional findings have not been reported in other published cases of Krabbe disease. No appreciable abnormal low attenuation in either the periventricular or deep white matter was seen when this finding was first detected, but this finding can persist into the late atrophy stage.

The etiology of symmetric density on CT has not been explained histologically, but it could represent transient alteration in the ratio of lipid, water, and protein [4] in both the gray matter and the periventricular white matter in response to the breakdown of myelin during the early and intermediate states of Krabbe disease. Analytic proof of events occurring at the tissue level during the early and intermediate stage of Krabbe disease is difficult to obtain. Since brain biopsy is not mandatory for diagnosis, in most cases, tissue is not available for biochemical analysis. However, from analysis of autopsy material in patients with Krabbe disease, water content is known to be increased markedly, while the myelin constituents, especially proteolipid protein, cerebroside, phospholipid, and cholesterol, are known to be decreased in the white matter with concomitant decrease of phospholipid in the gray matter after myelin breakdown. Moreover, the replacement of the normal brain cytoarchitecture by proliferated astroglial cells, modified macrophages, and globoid bodies is associated with alteration in the pattern of protein metabolism [4, 10]. Alteration in the lipid and protein metabolism also has been documented in a multitude of white- and gray-matter diseases [4].

Of the eight reported cases [5–9], including three of our own, a white-matter abnormality was not detected on early scans in five; this reflects the timing of the CT scan with respect to the pathologic progression of the disease. Likewise, the inconstant new finding of symmetric increased density in the thalami, body of the caudate nuclei, corona radiata, cerebellum, and brainstem in patients with Krabbe disease may also reflect the timing of the CT scan.

In one of our patients, a punctate part of the increased density was extremely dense, perhaps representing calcification or some other heavy metallic ion; no biopsy material was available for confirmation. There was no histologic documentation of calcification on the initial clinical and neuropathologic description by Krabbe in 1916 or in subsequent published reports. Alexander disease is the only leukodystrophy in which punctate areas of calcification in the periventricular white matter have been reported [11]. Calcification in the basal ganglia occurs in a wide variety of disease processes, including hypoparathyroidism, pseudohypoparathyroidism, carnitine deficiency, mitochondrial myopathy, Fahr disease, disseminated necrotizing leukoencephalopathy associated with metrotrexate therapy, perineonatal infection (TORCHS), extensive brain damage after anoxia/ischemia/hemorrhage in early life, carbon monoxide intoxication, and lead intoxication [12]. Our patients did not have clinical features or laboratory abnormalities that fell into these categories.

The CT features of the dysmyelinating and demyelinating diseases Krabbe disease, metachromatic leukodystrophy, Alexander disease, Canavan disease, adrenoleukodystrophy, and sudanophilic leukodystrophy are nonspecific at the end stage. However, there are certain distinguishing features at the acute stage that may guide the clinician in ordering the appropriate laboratory tests. The new findings discussed in our report should help with Krabbe disease. CT scans of patients with either Alexander disease or Canavan disease demonstrate low attenuation of white matter and macrocephaly in the absence of hydrocephalus. In Alexander disease, the abnormality is most prominent anteriorly. Of the various leukodystrophies, contrast enhancement has been reported only in Alexander disease and adrenoleukodystrophy [13–15]. In Alexander disease, contrast enhancement is localized in the caudate nuclei, anterior column of the fornices, and the subependymal white matter [11]. Enhancement in adrenoleukodystrophy type II usually involves the internal capsule, corpus callosum, corona radiata, and cerebral peduncles [14]. The CT findings of Alexander disease and adrenoleukodystrophy are sometimes typical enough that the diagnosis can be strongly suggested in the presence of supportive clinical signs and symptoms. However, a definitive diagnosis can be obtained only with brain biopsy. CT scans of patients with metachromatic leukodystrophy typically show periventricular low density, followed by atrophy at a later stage [16]. Diagnosis is confirmed by absence of arylsulfatase-A enzyme activity. Canavan disease and sudanophilic leukodystrophy can be confirmed only by brain biopsy. The diagnosis of Krabbe disease and metachromatic leukodystrophy is supported by the presence of peripheral neuropathy. Somewhat similar low attenuation of white matter also occurs in other childhood neurodegenerative disorders [6, 17], most but not all of which can be distinguished by the clinical context or biochemical tests.

ACKNOWLEDGMENTS

We thank Jeannie Leary for secretarial and editorial assistance. Case 3 was courtesy of D. Norman and T. H. Newton, University of California, San Francisco.

REFERENCES

1. Krabbe K. A new familial, infantile form of diffuse brain-sclerosis. *Brain* **1916**;39:73–114
2. Farrell DF, Swedberg K. Clinical and biochemical heterogeneity of globoid cell leukodystrophy. *Ann Neurol* **1981**;10:364–368
3. Dunn HG, Lake BD, Dolman CL. The neuropathy of Krabbe infantile cerebral sclerosis. *Brain* **1969**;92:329–344
4. Morrell P, Bornstein M, Raine C. Disease involving myelin. In: Seigel GH, ed. *Basic neurochemistry*. Boston: Little, Brown, **1976**:581–604
5. Barnes D, Enzmann D. The evolution of white matter disease as seen on computed tomography. *Radiology* **1981**;138:379–383
6. Kingsley DPE, Kendall BE. Demyelinating and neurodegenerative disease in childhood. *J Neuroradiol* **1981**;8:243–255
7. Heinz ER, Drayer BP, Haenggeli CA, Painter MJ, Crumrine P. Computed tomography in white matter disease. *Radiology* **1979**;130:371–378
8. Lane B, Carroll BA, Pedley TA. Computerized cranial tomography in cerebral diseases of white matter. *Neurology* (NY) **1978**; 28:534–544
9. Kendall BE, Kingsley D. The value of computerized axial tomography in craniocerebral malformations. *Br J Radiol* **1978**;51:171–190
10. Vanier UT, Svennerholm L. Chemical pathology of Krabbe's disease. *Acta Paediatr Scand* **1974**;63:494–500
11. Holland IM, Kendall BE. Computed tomography in Alexander's disease. *Neuroradiology* **1980**;20:103–106
12. Cohen CR, Duchesneau PM, Weinstein MA. Calcification of basal ganglia as visualized by CT. *Radiology* **1980**;134:97–99
13. Quisling RG, Andriola MR. Computed tomographic evaluation of the early phase of adrenoleukodystrophy. *Neuroradiology* **1979**;17:285–288
14. Di Chiro GD, Eiben RM, Manz HJ, Jacobs IB, Schellinger D. A new CT pattern in adrenal leukodystrophy. *Radiology* **1980**; 137:687–692
15. Duda EE, Huttenlocher PR. CT in adrenal leukodystrophy. *Radiology* **1976**;120:329–350
16. Buonanno FS, Ball MR, Laster W, Moody DM, McLean WT. CT in late infantile metachromatic leukodystrophy. *Ann Neurol* **1978**;4:43–46
17. Boltshauser E, Spiess H, Isler W. Computed tomography in neurodegenerative disorders in childhood. *Neuroradiology* **1978**; 16:41–43