Cerebral CT Findings in Methylmalonic and Propionic Acidemias

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The cerebral computed tomographic findings in two infants with methylmalonic acidemia and one infant and one adult with propionic acidemia are presented. Pertinent metabolic, clinical, and pathologic features of these genetic disorders of vitamin B_{12} (cobalamin) and biotin metabolism are reviewed briefly. Computed tomographic abnormalities consist of focal or diffuse deep cerebral hemisphere lucencies and diffuse loss of brain substance. These findings correlated well with the clinical and pathologic findings. The leukoencephalopathy in these uncommon autosomal recessive conditions appears to be due to ketoacidosis, which in some cases may be managed by vitamin supplementation.

Methylmalonic acidemia (MMA) and propionic acidemia (PA) are genetic disorders of amino acid metabolism. They both involve defective conversion of propionate to succinate, with clinical presentations early in life dominated by ketoacidosis without diabetes mellitus, sepsis, or other common cause [1–10]. The neurologic abnormalities in most patients can be attributed to the ketoacidosis. The final, specific diagnosis is biochemical, and early detection with proper therapy may permit normal neurologic development [2, 9]. Previous reports on MMA and PA have helped to increase the clinical awareness of these conditions [1–10]. Although a case of PA has been included in a general computed tomographic (CT) review of white-matter diseases [11], more specific and comprehensive reports on the cerebral CT findings in MMA and PA are lacking and prompted the present report.

Materials and Method

During a 5 year period, two patients with the clinical diagnosis of MMA and two patients with the clinical diagnosis of PA underwent CT. All studies were performed on an updated EMI 1005 scanner using a 60 sec scan time, 160 × 160 matrix, and 8 mm collimator.

Case Reports

Case 1

A 1-month-old boy had severe ketoacidosis and hyperglycinemia. Elevated levels of methylmalonic acid were found in urine and serum. No megaloblastic anemia was seen. Serum B_{12} was normal. CT showed diffuse leukoencephalopathy (fig. 1). The patient had a stormy clinical course with development of cirrhosis, ascites, and malnutrition. No response to vitamin B_{12} was noted. Death occurred at 4 years of age due to cirrhosis. Autopsy showed diffuse cerebral and cerebellar atrophy, most marked in the white matter.

Case 2

A 4-month-old girl had delayed development and spastic quadriparesis. Urine and serum

Received October 5, 1982; accepted after revision December 17, 1982.

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AJNR 4:955–957, July/August 1983
0195-6108/83/0404-0955 $00.00

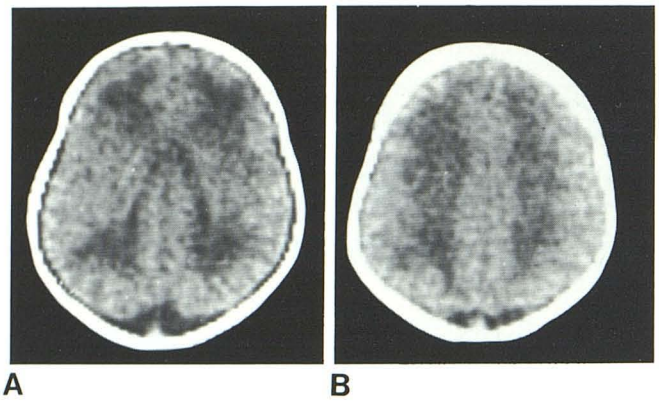


Fig. 1.—Case 1. CT at 1 month of age shows diffuse leukoencephalopathy.

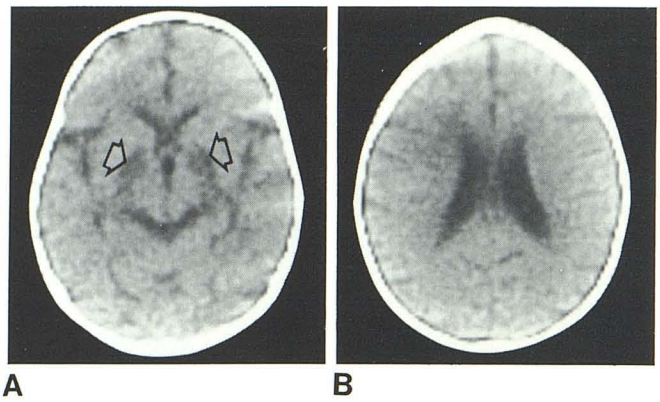


Fig. 2.—Case 2. CT at 1 year of age demonstrates decreased attenuation in posterior limbs of internal capsules (**A**, *arrows*), moderate diffuse loss of cerebral substance, and decreased attenuation in white matter of left frontal lobe (**B**).

analysis revealed elevated levels of methylmalonic acid, which were found to be responsive to vitamin B_{12} treatment. Pretreatment serum B_{12} levels were normal. There was no evidence of homocystinuria. CT at 12 months of age showed diffuse loss of cerebral substance and focal white-matter lucencies in the posterior limbs of the internal capsules (fig. 2). Follow-up scan 3 months later showed no significant change. The patient has been receiving outpatient care for severe mental retardation and spastic quadriparesis.

Case 3

A 2-month-old girl had ketoacidosis, hyperglycinemia, and spastic quadriparesis. Elevated propionic acid levels were found in urine and serum. CT at 3½ years of age showed diffuse cerebral atrophy (fig. 3). No clinical response to biotin or protein restriction was noted. Outpatient follow-up showed a stable clinical status. No further CT was done.

Case 4

A 17-year-old woman presented with mild mental retardation and headache. Elevated propionic acid levels were found in urine and serum. CT after intravenous infusion of 100 ml Conray-60 (meglumine iothalamate 60%) suggested a subtle lucency in the posterior limb of the right internal capsule (fig. 4). There was no pathologic contrast enhancement. No history to suggest transient ischemic attack or stroke was elicited. Outpatient follow-up included biotin therapy and protein restriction, without clinical change. No further CT was performed.

Discussion

Acquired vitamin deficiency can be produced by nutritional, absorptive, pharmacologic, or developmental interferences with vitamin utilization. In contrast, some individuals have a constant, specific requirement for a particular vitamin that differs from normal, either in requiring parenteral rather than oral vitamin administration or in requiring 10 to 10,000 times the quantity of vitamin that is recommended normally. The vitamin-dependent or vitamin-responsive conditions in such patients result from a genetically determined biochemical abnormality, which usually involves only a single reaction [10].

Of the inherited disorders of vitamin B_{12} metabolism, at least eight different human mutations have been identified, three of intestinal absorption, two of plasma transport, and three of tissue utilization. The last category constitutes the MMAs [10].

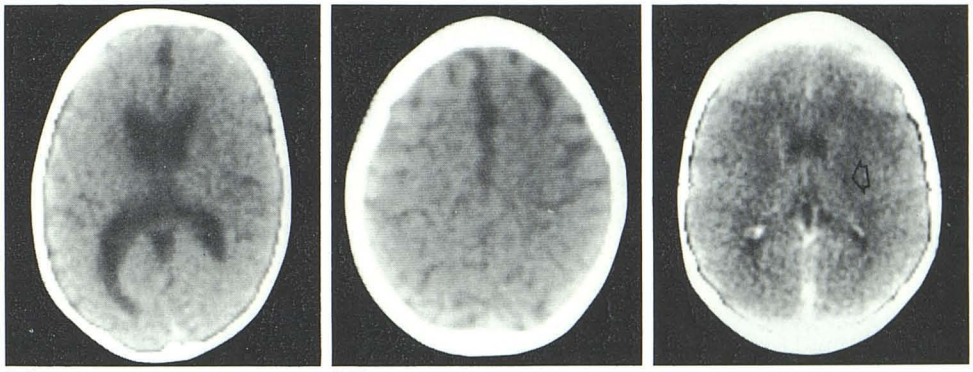
MMA usually presents in childhood with unexplained ketoacidosis and elevated levels of methylmalonic acid in blood and urine [4]. The biochemical deficit lies in deranged methylmalonic acid coenzyme A metabolism [5]. Two general subtypes exist, both with autosomal recessive inheritance patterns. The first subtype presents with a classic pattern of ketoacidosis, hyperglycinemia, and mental retardation. Both cobalamin (vitamin B_{12})-responsive and cobalamin-unresponsive forms of this subtype have been found [10]. Clinical management includes protein restriction and cobalamin supplementation. Simple cobalamin deficiency in infants and children is rare but must be ruled out early in the diagnostic workup [9]. The second subtype is associated with deranged sulfur amino acid metabolism, mental retardation, and no ketoacidosis. This subtype is better considered with homocystinuria [8] and is not discussed further in this report.

Biotin serves as a coenzyme in a number of ATP-dependent carboxylations. If there is a primary defect in the activity of the biotin-dependent enzyme propionyl-CoA carboxylase, the affected infants and children accumulate large amounts of proprionate in the blood (PA) and urine (propionic aciduria) [10]. The biochemical deficit appears to be inherited in an autosomal recessive pattern [7]. The clinical course of these patients has often been devastating, with neonatal ketosis, acidosis, failure to thrive, protein intolerance, and early demise. Both biotin-responsive and biotin-unresponsive forms have been reported [10]. Therapy includes protein restriction and careful treatment of secondary infections [2, 9].

MMA and PA have been associated with the older term

Fig. 3.—Case 3. CT at 3½ years of age shows moderate to severe diffuse cerebral atrophy.

Fig. 4.—Case 4. Contrast-enhanced CT at 17 years of age suggests subtle area of decreased attenuation in posterior limb of right internal capsule (*arrow*).



3A 3B 4

"ketotic hyperglycinemia," which is confusing and probably should be discarded not only because hyperglycinemia is not a specific or constant finding in MMA and PA, but it also erroneously suggests a primary abnormality of glycine metabolism in these conditions [6, 9].

For neuroradiologic purposes, MMA and PA can be considered together. These patients may be seen early in the clinical workup of unexplained ketoacidosis or after a specific biochemical diagnosis has been made. In our patients, the cerebral hemispheric white matter is affected most severely. Not surprisingly, mild CT abnormalities are associated with mild clinical impairment (case 4). The most profoundly affected patients (cases 1–3) demonstrate severe leukoencephalopathy and diffuse loss of cerebral substance. All our patients were examined on a 60 sec scanner, and it is conceivable that they may appear somewhat different on a newer type scanner. While none of our patients had a chronologically complete series of CT scans, one case of PA with CT scans at 2 weeks and 8 months of age has been reported previously [11]. The severe leukoencephalopathy of case 1 (fig. 1) was demonstrated early in life during a period of ketoacidosis, whereas the diffuse atrophy of case 3 (fig. 3) was seen in a patient with long-standing, perhaps "end-stage" disease. Furthermore, the autopsy performed in case 1, 4 years after CT had demonstrated severe leukoencephalopathy, showed severe, diffuse, predominantly white-matter atrophy. These findings all support the previously advanced hypothesis that leukoencephalopathy ultimately progresses to diffuse loss of white matter, with ventricular enlargement and eventual return of the remaining white matter to normal or nearly normal density on CT [11]. The reason for selective involvement of the posterior limbs of the internal capsules in cases 2 and 4 is unknown.

Intravenous administration of contrast material did not produce any contrast enhancement or contribute to making a specific diagnosis (case 4) [11]. Insufficient numbers of CT examinations are available to judge the possible role of CT in grading response to therapy.

ACKNOWLEDGMENT

We thank Sandra Ressler for assistance in manuscript preparation.

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