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CT and MR of the Brain in Disorders of the Propionate and Methylmalonate Metabolism

Jan Brismar and Pinar T. Ozand

PURPOSE: To present the CT and MR findings in children with propionic and methylmalonic acidemia. **METHODS:** Twenty-three new patients with methylmalonic and 20 with propionic acidemia were examined with CT and/or MR of the brain. In total 52 CT and 55 MR studies were done. Twenty-six previously published cases were also reviewed. **RESULTS:** The findings were similar in the two syndromes. During the first month of life the examinations were either normal or showed white matter attenuation. Later during the first year moderate or even severe widening of sulci and fissures was seen, especially in infants with propionic acidemia. During therapy, these changes often resolved, especially in the patients with methylmalonic acidemia. Mild to moderate delay in myelination was also a common finding in both disorders. Basal ganglia changes, predominately in the globus pallidus, were seen in five patients with methylmalonic acidemia and in two children with propionic acidemia; in two patients these changes were transient. **CONCLUSION:** Children who have methylmalonic or propionic acidemia, in addition to widening of cerebrospinal fluid spaces and some delay in myelination, also often show symmetric involvement of the basal ganglia.

Index terms: Acidemia; Brain, computed tomography; Brain, magnetic resonance; Brain, metabolism; Pediatric neuroradiology

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In inborn errors of metabolism, metabolic routes are blocked, resulting in an accumulation of intermediary products that sometimes causes severe neurologic symptoms. A major metabolic pathway passes via propionyl-coenzyme A (propionyl-CoA) through methylmalonyl-CoA to the tricarboxylic cycle. Different metabolic defects may block the breakdown of propionyl-CoA, causing propionic acidemia (PPA), or the breakdown of methylmalonyl-CoA, causing methylmalonic acidemia (MMA). These two disorders are both among the least rare of the organic acidemias; by 1989 more than 100 cases of each disease had been reported (1).

MMA and PPA are, like other organic acidemias, associated with cerebral complications. Reports on the neuroradiologic findings mainly consist of case reports: we found 13 reported patients with MMA (2–8) and 13 with PPA (2, 9–12).

We have had the opportunity to perform magnetic resonance (MR) and/or computed tomography (CT) of the brain in 20 new patients with PPA and 23 with MMA. The purpose of the present study was to combine our material with previously published cases, to study the time course for development of neuroradiologic findings, to study the distribution of lesions, and to follow the response to therapy.

Subjects and Methods

We have, in 4 years, verified the diagnoses of PPA in 29 patients and of MMA in 35. In all cases, the diagnoses were based on both gas chromatography and mass spectrometry and enzyme or isotope fixation studies.

All our cases of PPA were caused by propionyl-CoA-carboxylase deficiency. All but two of our MMA cases responded dramatically to cobalamin and thus belong

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either to the cobalamin A or cobalamin B variants; the two that did not respond were severe disease and probably belong to the group that lacks methylmalonyl-CoA mutase (for explanation see below).

In 20 of the patients with PPA and in 23 of the children with MMA we performed CT and/or MR of the brain on one or more occasions. Clinical data on these patients are summarized in Tables 1 and 2. The age at each examination is presented in Figures 1 and 2. In many of the patients, the initial study was done because of a family history, before any symptoms or signs had developed.

CT was performed with 10-mm-thick contiguous axial sections. Contrast enhancement (Ultravist, 2 mL/kg body weight) was used only in a few cases.

All MR examinations were done on a 1.5-T device using dual-echo T2-weighted (2000/40, 80/2 [repetition time/echo time/excitations]), T1-weighted (600/20/2) 7-mm-thick axial sections with 0- to 2.5-mm gap (depending on head size), and T1-weighted sagittal sections. In some of the MR figures, the signal intensity is slightly unequal from side to side for technical reasons.

Both the CT and the MR examinations were evaluated for prominence of ventricles, sulci, or fissures, and for the anatomic extent of increased white matter T2 signal (or delayed myelination), both subjectively graded as absent, slight, moderate, or severe.

Results

The results are summarized in Tables 1 and 2. Although only 3 of the patients with PPA were diagnosed after 9 months of age, the median age for diagnosis in the MMA group was 12 months when those diagnosed as newborns, because of family history, are excluded. In both diseases, the children were often small, with small heads at diagnosis. The height was -2 SD or less in 10 of 20 children with PPA, and in 14 of 23 with MMA, head circumference was -2 SD or less in 13 of the children with PPA and in 10 of those with MMA. Clinical findings ranged from normal to severe hypotonia and choreoathetosis in both diseases. At the diagnosis, many of the children already had been admitted to the hospital multiple times, often also to intensive care units. One boy with MMA had 11 admissions (3 of those to intensive care units) before diagnosis at 16 months of age; one girl with PPA was admitted 6 times before diagnosis at 15 months. The compliance with therapy was variable. In only about half the patients was the compliance listed as good or excellent; in one third it was poor or none. The finding of reduced height or head circumference in most patients remained the same despite therapy; the clinical

findings improved in 7 of the children with PPA and in 9 of the patients with MMA. Two patients with PPA and 5 with MMA died during the observation period; in another 3 patients with PPA the condition worsened; in 6 patients with each disease the clinical findings were unchanged. The deaths were mainly in patients not compliant to the therapy.

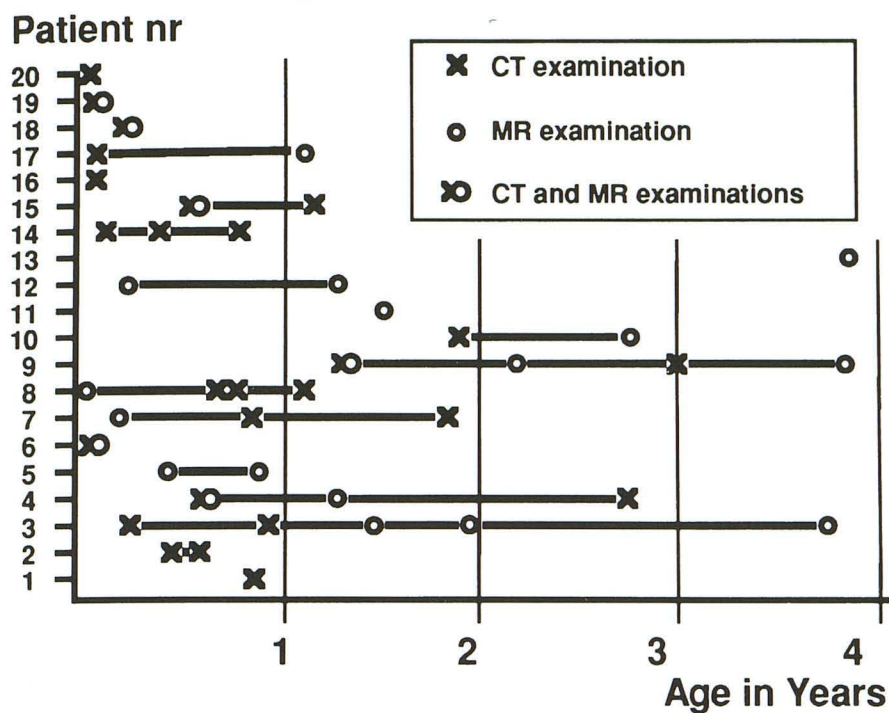
The size of ventricles and sulci was normal during the first month of life in both diseases, but although in the infants with MMA the white matter also appeared normal, in most infants with PPA low-density white matter changes were seen. Later during the first year, prominence of ventricles and sulci was seen in all patients, but white matter changes were less frequently diagnosed. Some delay in myelination was seen in most children with MMA examined during the second year of life; this was less obvious in the infants with PPA. In children examined after 2 years, the findings were less pronounced, and in several, previously delayed myelination or prominent ventricles and sulci had normalized. As is evident from the tables, there seems to be a correlation between the degree of compliance to therapy and the severity of the radiologic findings. In some patients, despite therapy, a large number of hospital admissions, also to intensive care units, was needed for the treatment of the disease. Astonishingly, despite this fact, neuroradiologic findings were often normal or only mildly abnormal. Basal ganglia changes were seen in seven patients and do not seem to correlate clearly either to severity of clinical findings, to other radiologic abnormalities, to compliance to therapy, or even to therapeutic problems as documented by hospital admissions after the diagnosis. Although in MMA the basal ganglia lesions in all but one patient were limited to globi pallidi, in the two patients with PPA the changes involved also the caudate heads and the putamina.

Discussion

The incidence of MMA from one neonatal screening program has been estimated to be 1 in 48 000 (13), but when less-severe cases are also included, it may be as high as 1 in 25 000 (14). In the Massachusetts screening program only 1 patient with PPA was found among 331 143 infants screened (15). In a paper describing 326 patients with inherited metabolic diseases, 21 cases of PPA compared with 31 of

Propionic acidemia

Fig 1. Age at CT and MR examinations in 20 patients with PPA.



Methylmalonic acidemia

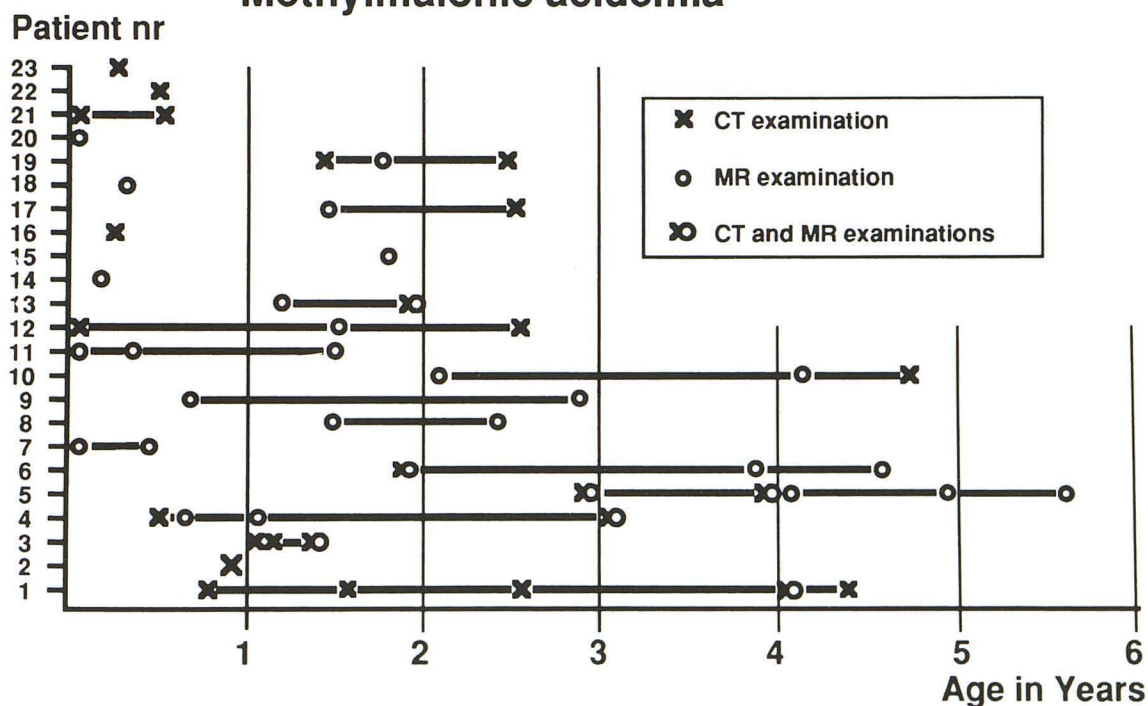


Fig 2. Age at CT and MR examinations in 23 patients with MMA.

TABLE 1: Clinical data and brain MR and/or CT findings in 20 patients with PPA

Patient	Sex/Age at Diagnosis	Clinical Findings at Diagnosis	Compliance with Diet/ Medication	Hospital Admissions before/after Diagnosis (of Those, Intensive Care Unit Admissions)	Age at Last Visit (Age at Death)	Findings at Last Visit or at Death	CT and MR Findings						Basal ganglial lesions		
							Sulci, fissures, ventricles		Subcortical white matter						
							<1 mo	1-11 mo	1 y	≥2 y	<1 mo	1-11 mo		1 y	≥2 y
1	F/9 mo	Height and HC -4 SD, severe hypotonia, severe chorea, brain stem blind and deaf	...	4(0)/...	(9 mo)	Died shortly after diagnosis	-	+	-	-	-	N	-	-	None
2	M/7 mo	Height or HC not known, stupor, myoclonic seizures	.../good, resp	2(1)/0	(12 mo)	Height or HC not known, opisthotonus, blind, deaf, clonus	-	++	-	-	-	N	-	-	None
3	M/4 mo	Height 75th percentile, HC -2 SD, severe developmental retardation	Excellent	2(0)/2(0)	5 y 7 mo	Height 50th, HC 10th percentile, mild developmental retardation, deaf	-	++→++	N	N	-	++→++	++→++	N	None
4	M/8 mo	Height -4 SD, HC -3 SD, severe hypotonia	Poor/moderate, resp	3(2)/4(2)	4 y	Height -3 SD, HC -4 SD, severe hypotonia, chorea	-	++	+	+	-	+	+	N	None
5	F/3 mo	Height and HC -2 SD, blind, nystagmus, severe hypotonia	None	3(2)/2(2)	(16 mo)	Height and HC -3 SD, unchanged clinical findings	-	N	→+	-	-	N	-	-	None
6	F/1 mo	Height 25th percentile, HC -3 SD, stupor, hypotonic, coma	...	2(2)/...	(1.5 mo)	Died shortly after diagnosis	N	-	-	-	++	-	-	-	None
7	F/1 mo	Height and HC -2 SD, coma, severely impaired	Poor	1(1)/1(1)	3 y	Height and HC -4 SD, blind, deaf, no milestone	-	++	++	-	-	N	N	-	None
8	M/1 mo	Height -3 SD, HC -2 SD, hypotonia	Fair	1(0)/9(3)	(15 mo)	Height -6 SD, HC -4 SD, intracranial bleed led to hydrocephalus; poliomyelitis, severe hypotonia	N	++	++	-	N	N	N	-	None
9	F/15 mo	Height -4 SD, HC -5 SD, severe progressive pyramidal tract disease, choreoathetosis	None/fair, resp	6(0)/0	3 y 10 mo	Height -3 SD, HC -2 SD, moderate hypotonia, hemiplegia, dysconjugate gaze	-	-	++	++	-	-	++→	N	Caudate, globus pallidus, putamen

TABLE 1: Continued

Patient	Sex/Age at Diagnosis	Clinical Findings at Diagnosis	Compliance with Diet/ Medication	Hospital Admissions before/after Diagnosis (of Those, Intensive Care Unit Admissions)	Age at Last Visit (Age at Death)	Findings at Last Visit or at Death	CT and MR Findings						Basal ganglial lesions		
							Sulci, fissures, ventricles		Subcortical white matter		Basal ganglial lesions				
							<1 mo	1-11 mo	1 y	≥2 y		<1 mo		1-11 mo	1 y
10	M/18 mo	Height −3 SD, HC −2 SD, severe hypotonia, severely delayed development	Fair	4(1)/3(0)	3 y 8 mo	Height −4 SD, HC 50th percentile, moderate hypotonia	−	−	+	+	−	−	N	+	None
11	F/6 mo	Height 75th and HC 10th percentile, hypotonia, severe choreoathetosis	Excellent	1(1)/0	2.5 y	Height 90th and HC 50th percentile, hypotonia, mild chorea	−	−	+	−	−	−	N	−	Caudate, globus pallidus, putamen
12	F/4 mo	Height and HC 40th percentile, stupor, hypotonia, clonus	Good	3(0)/2(0)	2 y	Height 25th and HC 5th percentile, mild hypotonia	−	++	N	−	−	N	+	−	None
13	F/3 y 8 mo	Height and HC 50th percentile, demented, severe spastic quadriplegia	None/excellent, resp	1(0)/0	5 y 6 mo	Height and HC 90th percentile, normal	−	−	−	N	−	−	−	N	None
14	M/1 wk	Height and HC −2 SD, slight hypotonia	Good	2(1)/2(0)	22 mo	Height and HC unchanged, almost normal	−	+++	→++	−	−	−	N	−	None
15	F/7 mo	Height and HC −3 SD, hypotonia	Good	2(1)/4(0)	26 mo	Height and HC −2 SD, same findings	−	++	++	−	−	+	N	−	None
16	F/4 mo	Height −3 SD, HC −4 SD, hypotonia	Good	2(1)/5(3)	9 mo	Height −5 SD, HC −6 SD, severe hypotonia, severe choreoathetosis	N	−	−	−	+	−	−	−	None
17	F/1 mo	Height 10th and HC 5th percentile, hemiplegia	Good	2(1)/1(0)	15 mo	Height and HC unchanged, normal	N	−	+	−	++	−	+	−	None
18	M/2 mo	Height 25th percentile, HC −2 SD, blind, hypotonia, decreased reflexes	Poor	2(1)/2(0)	9 mo	Height 90th percentile, HC no change, unchanged findings	−	+	−	−	−	N	−	−	None
19	M/1 wk	Height and HC 40th percentile, cortical grasp, mild hypotonia	Excellent	1(1)/0	4 mo	Too early to assess	N	−	−	−	+	−	−	−	None
20	M/5 d	Head 75th and HC 50th percentile, mild hypotonia	...	2(1)/0	5 wk	Too early to assess	N	−	−	−	N	−	−	−	None

Note.—HC indicates head circumference; N, normal findings; +, slight changes; ++, moderate changes; +++, severe changes; -, no study during the age interval.

TABLE 2: Clinical data and brain MR and/or CT findings in 23 patients with MMA

Patient	Sex/Age at Diagnosis	Clinical Findings at Diagnosis	Compliance with Diet/ Medication	Hospital Admissions before/after Diagnosis (of Those, Intensive Care Unit Admissions)	Age at Last Visit (Age at Death)	Findings at Last Visit or at Death	CT and MR Findings							
							Sulci, fissures, ventricles		Subcortical white matter					
							<1 mo	1-11 mo	1 y	≥2 y	<1 mo	1-11 mo	1 y	≥2 y
1	M/10 mo	Height -4 SD, HC 50th percentile, pyramidal signs	Excellent	2(2)/12(2)	7 y	Height -5 SD, HC no change, hemiplegia	-	++	+	N	N	N	N	Basal ganglia lesions
2	M/11 mo	Height and HC unknown, hypotonia central hyperventilation, extrapyramidal signs	None	1(1)/2(2)	(12 mo)	No change	-	++	-	-	N	-	-	None
3	F/1 y	Height -3 SD, HC 90th percentile, mild pyramidal signs	Excellent	3(1)/1(0)	5.5 y	Height 50th percentile, HC no change, normal	-	++→+	+	-	N	+	-	None
4	F/7 mo	Height -4 SD, HC -4 SD, severe hypotonia, poor sucking	Excellent	1(1)/2(0)	4.5 y	Height -5 SD, HC -2 SD, mild chorea	-	++→++	N	N	N	++	+	None
5	M/2 y 10 mo	Height -3 SD, HC -2 SD, normal neurology	Good	5(5)/9(1)	6 y 10 mo	Height -5 SD, HC no change, normal neurology	-	-	-	+	-	-	++	Transient basal ganglia
6	F/2 y	Height -3 SD, HC -5 SD, hypotonia, clonus	Fair	7(1)/16(2)	6 y	Height -2 SD, HC -3 SD, normal	-	-	-	+	-	-	+	None
7	M/birth	Small with small head, hypotonia	Fair	...	(1 y)	Height -4 SD, HC 40th percentile, hypotonia	N	+	-	-	N	-	-	None
8	M/16 mo	Height -6 SD, HC -2 SD, optic atrophy, hypotonia, choreoathetosis mild mental retardation	Fair	11(3)/4(0)	30 mo	Height -3 SD, HC 25th percentile, optic atrophy, otherwise normal	-	-	+	N	-	+	+	None
9	F/17 mo	Height -4 SD, HC 50th percentile, hypotonia, mild mental retardation	Poor	1(1)/8(2)	(3.5 y)	Height and HC unchanged, normal	-	+	-	N	-	-	N	Globus pallidus
10	F/2 y 10 mo	Height 25th and HC 50th percentile, no neurology	Excellent	2(1)/0	6 y	Unchanged normal	-	-	-	N	-	-	N	None
11	M/birth	Height 10th and HC 40th percentile, no neurology	Excellent	1(1)/0	3.5 y	Unchanged normal	N	+	+	-	N	+	-	None

TABLE 2: Continued

Patient	Sex/Age at Diagnosis	Clinical Findings at Diagnosis	Compliance with Diet/ Medication	Hospital Admissions before/after Diagnosis (of Those, Intensive Care Unit Admissions)	Age at Last Visit (Age at Death)	Findings at Last Visit or at Death	CT and MR Findings						Basal ganglial lesions		
							Sulci, fissures, ventricles		Subcortical white matter						
							<1 mo	1-11 mo	1 y	≥2 y	<1 mo	1-11 mo		1 y	≥2 y
12	M/9 d	Height -2 SD, HC 25th percentile, severe encephalopathy	Fair	1(1)/0	3 y	Height -3 SD, HC -2 SD, normal	N	-	+	N	-	+	N	None	
13	M/1 y	Height 50th percentile, HC -3 SD, no neurology	None	2(1)/4(1)	(2.5 y)	Height and HC unchanged, hemiplegia	-	-	+	+	-	-	+	++	None
14	M/3 mo	Height and HC 25th percentile, hypotonia	...	1(1)/...	...	...	-	+	-	-	-	N	-	-	None
15	F/3 d	Height and HC -2 SD, hypotonia, seizures	Fair	1(1)/9(0)	3.5 y	Height -3 SD, HC no change, normal	-	-	+	-	-	-	+	-	None
16	F/3 mo	Height -3 SD, HC -4 SD, severe pyramidal signs, severe dysmorphia	None	2(1)/1(1)	(6 mo)	No change	-	++	-	-	-	N	-	-	None
17	F/12 mo	Height -5 SD, HC -3 SD, severe hypotonia, choreoathetosis	Excellent	3(2)/2(0)	34 mo	Height -4 SD, HC -2 SD, mild hypotonia	-	-	N	N	-	-	+	+	Globus pallidus
18	M/7 d	Height and HC 25th percentile, no neurology	Excellent	1(1)/0	2 y	No change	-	++	-	-	-	N	-	-	None
19	M/14 mo	Height -6 SD, HC 50th percentile, severe hypotonia, severe choreoathetosis	Excellent	5(4)/0	36 mo	Height -3 SD, HC no change, mild hypotonia	-	-	+	N	-	-	+	N	Globus pallidus
20	F/birth	Height and HC 50th percentile, no neurology	...	1(1)/...	...	...	N	-	-	-	N	-	-	-	None
21	F/5 d	Height 25th and HC 50th percentile, hypotonia	Poor	2(1)/4(1)	18 mo	Height -4 SD, HC -2 SD, mild hypotonia	N	+	-	-	N	N	-	-	None
22	M/6 mo	Height -3 SD, HC -2 SD, severe midline hypotonia, increased deep tendon reflexes	Poor	3(2)/2(1)	20 mo	Height and HC -4 SD, hypotonia	-	++	-	-	-	N	-	-	None
23	F/5 d	Height 25th and HC 50th percentile, hypotonia	Excellent	2(1)/3(1)	(14 mo)	No change	-	+	-	-	-	N	-	-	None

Note.—HC indicates head circumference; N, normal findings; +, slight changes; ++, moderate changes; +++, severe changes; -, no study during the age interval.

MMA were diagnosed (16), suggesting that the incidence of PPA should be somewhat lower than that of MMA, in the range of 1 in 35 000 to 1 in 70 000.

Consanguineous marriages are very common in Saudi Arabia, and many disorders inherited in an autosomal recessive mode, such as PPA and MMA, are therefore present with much higher prevalence than reported from western countries. The clinical features of PPA and MMA are somewhat similar. Both diseases are characterized by failure to feed, frequent vomiting, compensated to overt metabolic acidosis, and frequent infections. However, the acidosis is almost always very severe and resistant to treatment in MMA and milder and more easy to manage in PPA. Although both diseases cause central hypotonia, this is usually very severe in PPA and milder in MMA. PPA almost always causes immunodeficiency and severe thrombocytopenia during times of metabolic crisis; such manifestations are much less apparent in MMA. Both diseases cause acute metabolic crises

periodically, at which time the central nervous system findings of pyramidal tract signs worsen, and seizures appear, frequently in association with acidosis and hyperammonemia. If not diagnosed and treated promptly, the condition eventually will progress into irretractable coma, and the patient will die (1, 17–20).

The propionate-methylmalonate metabolism is summarized in Figure 3. The amino acids isoleucine, valine, and threonine, the odd-chain fatty acids, and the side chain of cholesterol are, through different intermediate steps, metabolized to propionyl-CoA. The further breakdown of propionyl-CoA to methylmalonyl-CoA depends on the enzyme propionyl-CoA-carboxylase, which for its action needs biotin as cofactor. PPA may be caused either by a lack of propionyl-CoA-carboxylase or by biotin deficiency. In such metabolic blocks, alternative pathways are used, resulting in accumulation of different metabolites. Biotin deficiency, in addition to causing PPA, also blocks the function of other carboxylases, causing multiple carboxy-

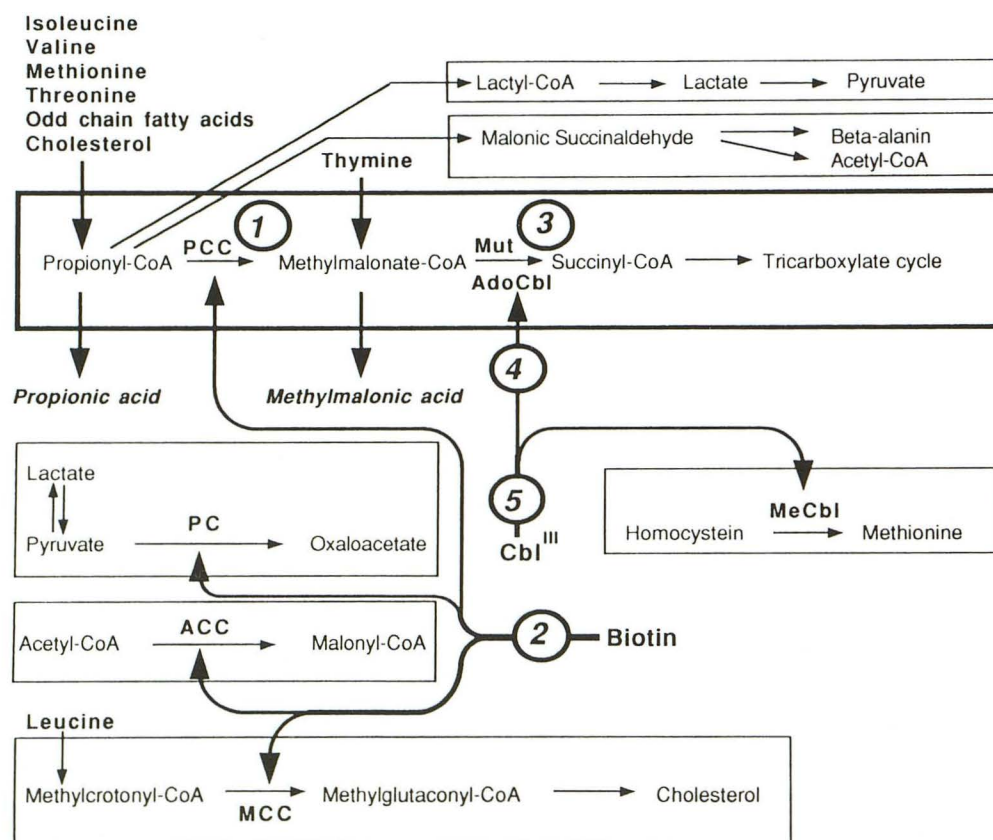


Fig 3. Schematic presentation of the propionate and methylmalonate metabolism. For details see "Discussion." Numbers 1 to 5 denote possible metabolic blocks: 1, propionyl-CoA carboxylase deficiency; 2, biotin deficiency; 3, methylmalonyl-CoA mutase deficiency; 4, mutations late in adenosylcobalamin synthesis (cobalamin A or cobalamin B mutations); and 5, mutations early in the synthesis also affecting methylcobalamin.

lase deficiency. Biotin deficiency will not be further discussed. MMA is caused by a block of the metabolism of methylmalonate-CoA to succinyl-CoA either from lack or deficiency of the enzyme methylmalonyl-CoA mutase or from a lack of the necessary coenzyme adenocobalamin. Deficiency of the mutase causes a milder form of disease than a total lack. Lack of adenocobalamin may be caused by metabolic defects at different stages of its synthesis. Defects at a late stage (cobalamin A and cobalamin B defects) cause only MMA; defects at an early stage, which also cause homocystinuria, are beyond the scope of this article.

The age at presentation in patients with MMA differs depending on the underlying defect (1, 19, 21). Whereas 80% of the children with a total lack of mutase become ill during the first week and 90% during the first month of life, the majority of patients with partial methylmalonyl-CoA mutase deficiency or with adenocobalamin defects present after the first month (20). Except 7 patients, all 35 cases of MMA seen at our hospital presented with symptoms after 1 month of age. Typically, patients with PPA present within the first week of life. However, in some patients the disease manifests itself in late infancy and childhood, often in association with a metabolic stress such as respiratory infections or gastroenteritis. There are individuals who have no clinical evidence but nonetheless are diagnosed as having a total lack of propionyl-CoA-carboxylase because of family history. (1, 11, 17). The reason behind this variety of presentations for the same enzyme defect is not understood. Also, some children with MMA caused by partial methylmalonyl-CoA mutase deficiency may develop completely normally and remain asymptomatic (22).

Essentially, the treatment for both diseases consists of restriction of proteins while maintaining adequate general nutrition. Patients with MMA with adenocobalamin defects respond dramatically to cobalamin. The treatment for MMA consists of a formula restricted in L-isoleucine:L-carnitine (100–200 mg/kg per day), during the acute phase daily intramuscular injections of 1 mg of hydroxycobalamin, and in the chronic phase 0.5 mg of cyanocobalamin daily as nasal spray. For PPA the therapy is a formula restricted in L-isoleucine and L-valine:biotin (10 mg/kg per day) and L-carnitine (100–200 mg/kg per day). Even with treatment, patients

may have acute metabolic crises during minor infections and after not eating.

The neuroradiologic findings were similar in our patients with PPA and MMA but were usually more severe in those with PPA. This was obvious even in the neonatal period, with all but one of the infants with MMA being relatively asymptomatic and identified mainly because of their family history. Two of the five infants with MMA examined during the first month of life were clinically healthy, two had slight muscular hypotonia, and only one had severe encephalopathy. Although all five of these patients had normal CT or MR findings, only two of six infants with PPA examined with CT or MR of the brain during the same period of life had normal-appearing white matter. Two had mild and one had moderate white matter abnormalities; the sixth displayed severe changes with necrosis of subcortical white matter (case 6; Fig 4). All six had normal-size ventricles and sulci.

Later during the first year of life, the sulci and fissures were widened in all 13 infants with MMA and in all 11 with PPA that were studied: markedly in 1 with MMA and in 3 with PPA, moderately in 7 with MMA and in 8 with PPA. Three of the 13 children with MMA had initial normal findings. In one child with PPA, shunt-requiring hydrocephalus developed secondary to intracranial bleeding caused by thrombocytopenia. All but 3 infants, who had PPA, had normal-appearing white matter. Whereas all 4 infants with MMA in this group who were diagnosed and treated with diet and medication since the neonatal period had only slight prominence of the cerebrospinal fluid (CSF) spaces, 6 of 7 diagnosed later had moderate or severe (1 patient) changes. Again, findings were more severe in the infants with PPA: all 3 children diagnosed and treated from the first month of life, who were studied during this age interval, had severe widening of the CSF spaces despite the early start of therapy.

Mild delay in myelination is difficult to identify during the first year of life. A delay in myelination was verified in 9 of 10 children with MMA studied during the second year of life, mild in 8 and moderate in one. At a repeat study after 2 years of age myelination had improved in 3 of 7 of these children. Also, the widening of the extracerebral CSF spaces subsided with age. Eight of 11 children with MMA studied between 2 and 6 years of age had normal sulci and fissures; in 6 children previously widened sulci

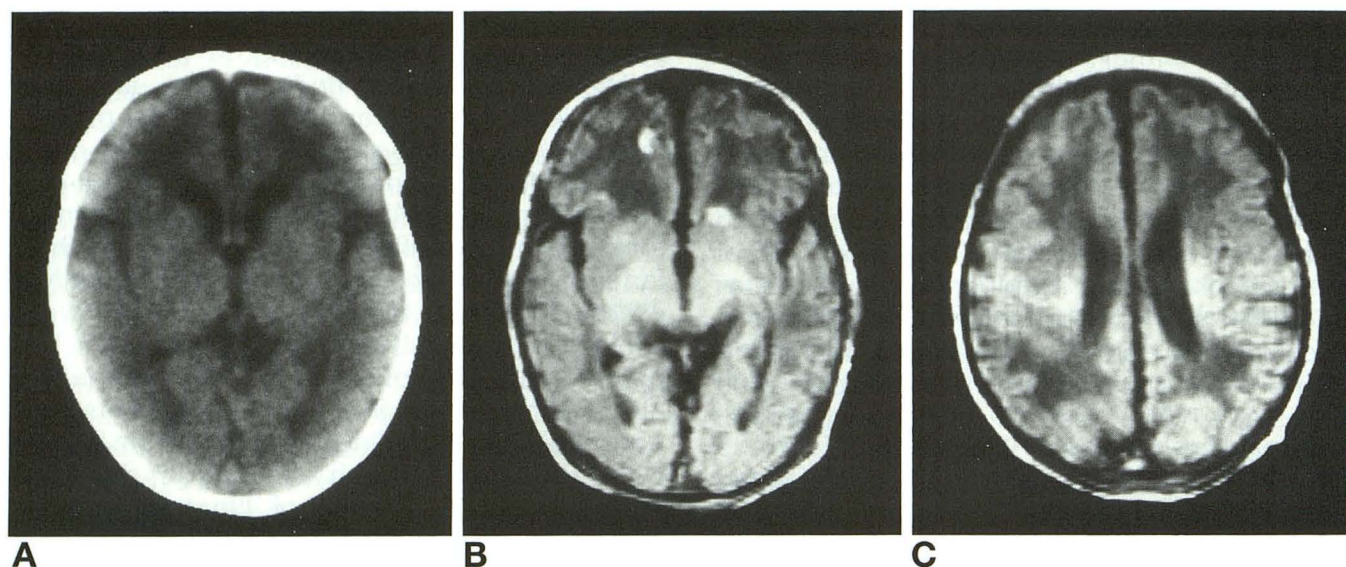


Fig 4. One-month-old girl with PPA (case 6): microcephaly, muscular hypotonia, stupor, and coma.

A, CT shows marked decrease in attenuation of subcortical white matter.

B and C, MR (T1-weighted) shows signs of white matter necrosis with bilaterally small frontal hemorrhages.

had returned to normal. In only 1 child an impairment, with progression of the white matter abnormalities, was observed. This child later died in a neglected MMA coma; his parents were noncompliant with therapy. Five patients with PPA were studied after the second year of life (Fig 5): in 3 patients, previously delayed myelination had normalized; in one patient mild T2 white matter changes had developed; and in the fifth patient the initial MR at almost 4 years of age was normal despite severe clinical symptoms. Two of these 5 children had normal ventricles and sulci, 3 slightly or moderately dilated.

One reason for the difference in severity of neuroradiologic findings between our patients with PPA and MMA may be that all but 2 of our children with MMA had mild variants of the disease (probably cobalamin A or cobalamin B defects) that respond well to cobalamin; they therefore initially had fewer and less-severe metabolic crises than the patients with PPA. Despite this fact, basal ganglia lesions were more common in the MMA group. No obvious correlation was found between the severity of the disease and the occurrence of basal ganglia changes. Although seen in only 1 of 12 patients with MMA examined between 1 month and 1 year of age, basal ganglia lesions were present in 5 of 10 children older than 28 months. In 1 child the lesions involved the putamina and were transient (case 5, Fig 6); CT and MR at 3

years of age demonstrated moderate subcortical white matter disease sparing the most peripheral white matter; at 4 years the putamina were bilaterally swollen and of irregularly, markedly increased T2 intensity. A repeat MR 3 weeks later showed normalization of the basal ganglia changes and some improvement of the subcortical white matter disease. In the remaining 4 children, symmetrical basal ganglia necrosis with volume loss was demonstrated; in all only the globi pallidi were involved (case 19, Fig 7). In 2 of the patients the necrosis was present at the first examination (cases 9 and 19, at 8 and 17 months of age, respectively). One child (case 17) had a normal MR at 17 months and showed basal ganglia necrosis 1 year later; one (case 1) had several normal CT studies up to 2.5 years and at 4 years had developed necrosis.

Basal ganglia lesions were seen in two of our patients with PPA. In one infant, an MR study at 1.5 years of age demonstrated increased T2 intensity within the globus pallidus, the putamen, and the caudate nucleus bilaterally (case 11, Fig 8). In the second child the first CT and MR examinations at 16 months (case 9, Fig 5) showed low-density, high-T2 intensity swollen globi pallidi, and marked prominence of sulci and fissures and some delay in myelination. Ten months later the changes in the globi pallidi were less prominent, but increased T2 intensity was now also present in the putamina and cau-

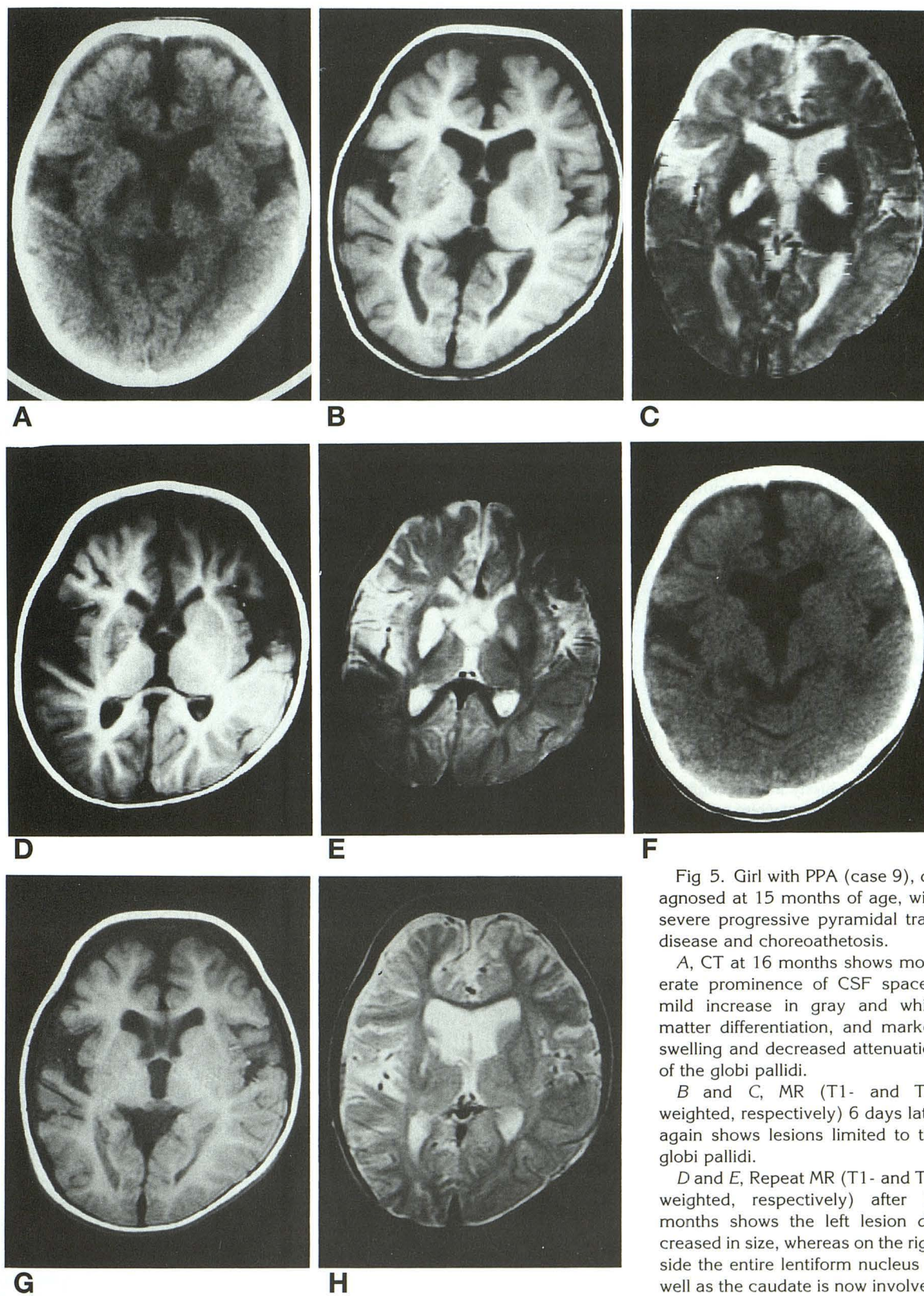


Fig 5. Girl with PPA (case 9), diagnosed at 15 months of age, with severe progressive pyramidal tract disease and choreoathetosis.

A, CT at 16 months shows moderate prominence of CSF spaces, mild increase in gray and white matter differentiation, and marked swelling and decreased attenuation of the globi pallidi.

B and C, MR (T1- and T2-weighted, respectively) 6 days later again shows lesions limited to the globi pallidi.

D and E, Repeat MR (T1- and T2-weighted, respectively) after 10 months shows the left lesion decreased in size, whereas on the right side the entire lentiform nucleus as well as the caudate is now involved.

F, CT after another 10 months

fails to demonstrate any basal ganglia lesion, and also the widening of the CSF spaces is less prominent.

G and H, MR (T1- and T2-weighted, respectively) 10 months later shows small high T2 residues within the right lentiform nucleus and caudate head; the right lentiform nucleus also has lost volume.

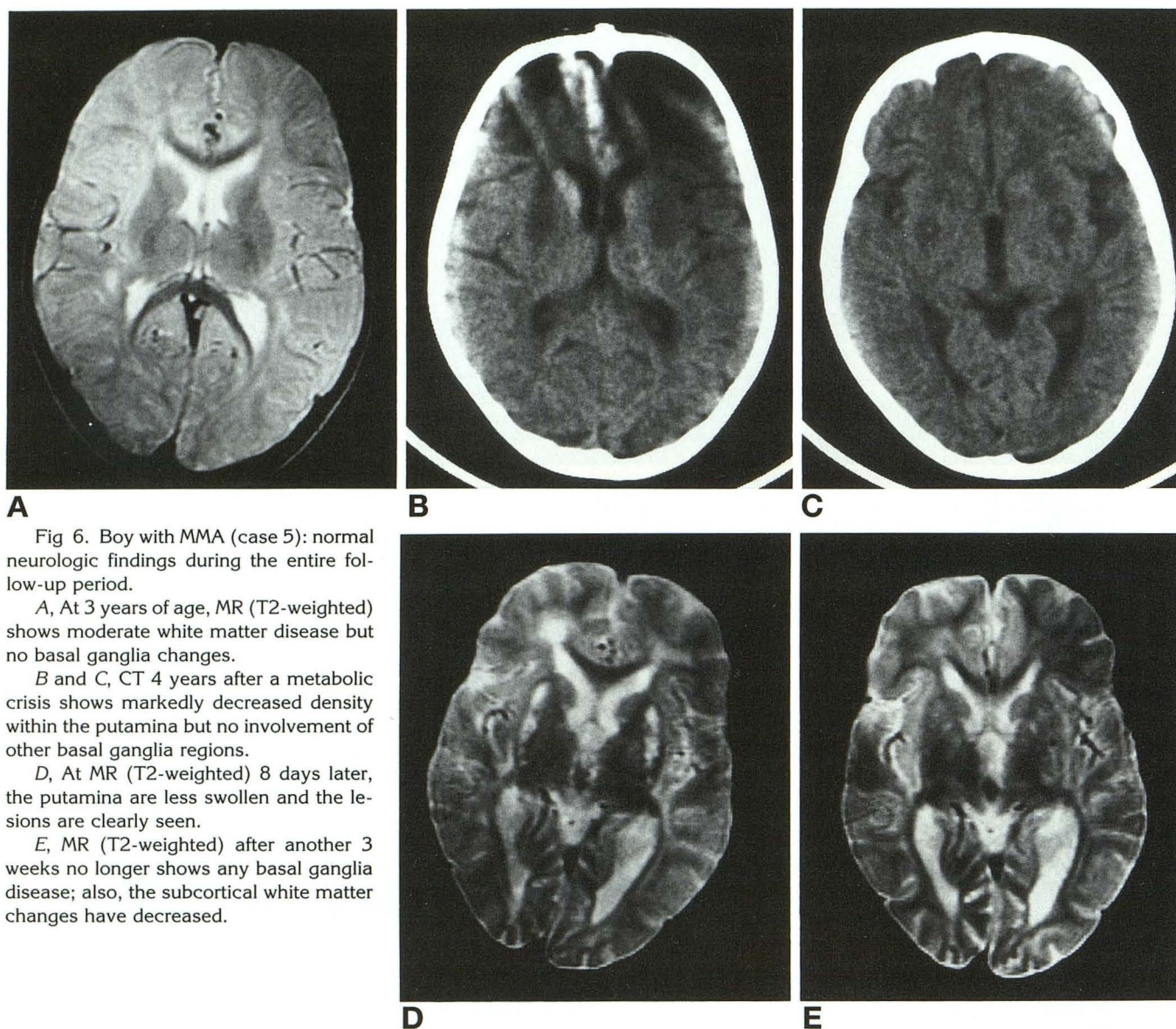


Fig 6. Boy with MMA (case 5): normal neurologic findings during the entire follow-up period.

A, At 3 years of age, MR (T2-weighted) shows moderate white matter disease but no basal ganglia changes.

B and C, CT 4 years after a metabolic crisis shows markedly decreased density within the putamina but no involvement of other basal ganglia regions.

D, At MR (T2-weighted) 8 days later, the putamina are less swollen and the lesions are clearly seen.

E, MR (T2-weighted) after another 3 weeks no longer shows any basal ganglia disease; also, the subcortical white matter changes have decreased.

date heads bilaterally. At a CT study another 10 months later no basal ganglia disease was identified, but a repeat MR after 10 months again showed a slitlike lesion in the right globus pallidus (Fig 5). This illustrates the difference in sensitivity between the two imaging modalities; the lesion was probably present all the time.

We found CT and MR results reported from 13 patients with PPA and 13 with MMA (2–10, 17, 18); MR was performed in 1 child with PPA (17) and 2 children with MMA (7, 8). The findings have been similar to those in our series. A report on the CT findings in a patient with PPA appeared in 1981 (9): a CT scan at 2 weeks of age showed diffusely decreased attenuation of the white matter; at 8 months white matter ap-

peared normal, but features of cerebral atrophy were present. Only two of the patients with MMA we found in the literature were examined before 1 year of age. In one infant examined at 1 month of age marked white matter edema was present (2); in 1 asymptomatic sibling to a patient with MMA studied at 9 months, CT findings were normal (7). As in our material, the changes were less obvious in older children: mild to moderate atrophy was reported in 4, and mild white matter changes in 2 of 5 children with MMA studied during the second year of life (2–4, 6), but only 2 of 7 children studied with CT of the brain later during childhood showed mild atrophy, and none showed white matter changes (4–8).

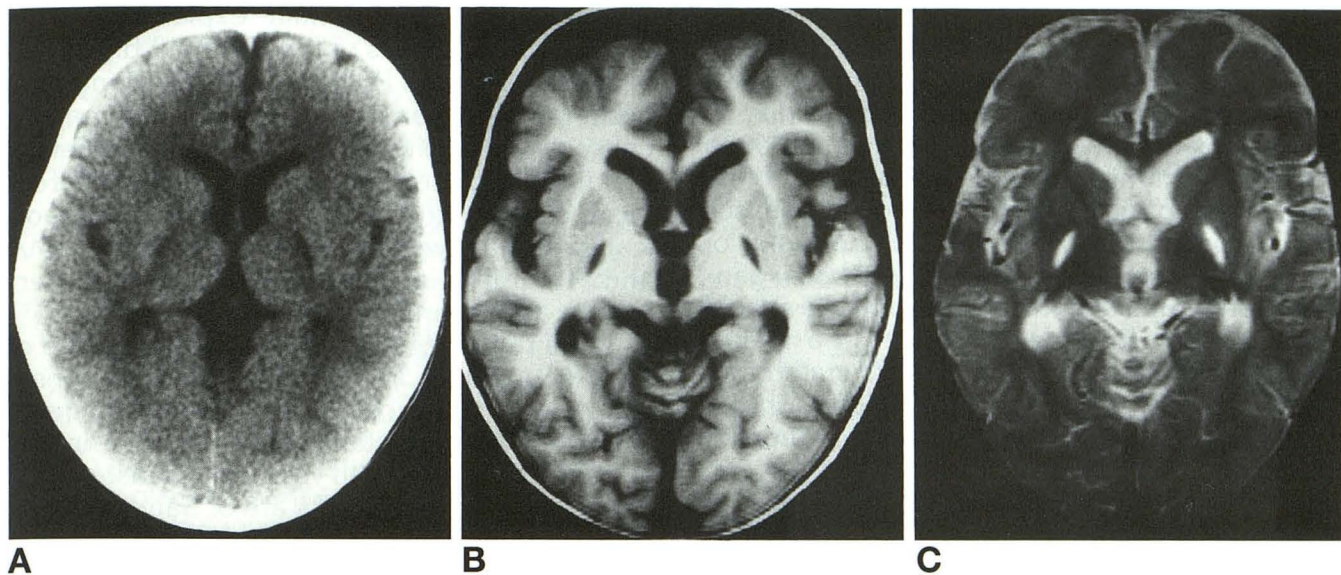


Fig 7. Boy with MMA (case 19): muscular hypotonia and severe choreoathetosis.

A, CT at 17 months of age shows slight prominence of CSF spaces and slightly decreased attenuation within the globus pallidus, bilaterally.

B and C, MR (T1- and T2-weighted, respectively) beautifully demonstrates very well demarcated necrotic lesions with loss of volume in the globi pallidi and also shows mild prominence of CSF spaces. Other sections documented slight white matter disease.

Autopsy findings in two infants with PPA who died during the neonatal period have been reported (10, 23, 24). In a 12-day-old infant with a fatal cerebellar hemorrhage, also seen at CT, patchy subcortical demyelination of subcortical white matter, status spongiosus of the globus pallidus and internal capsule, and marked loss of deep cerebellar subcortical myelinated fibers with spongy necrosis was found (10, 24). In a 26-day-old neonate, who had died from metabolic acidosis, microscopic examination of the brain demonstrated diffusely vacuolated myelin

of the posterior limb of the internal capsule, globus pallidus, the ascending and descending fibers of the brain stem, the tegmentum, and the posterior columns of the spinal cord (23). Vacuolization of the medial lemniscus, superior cerebellar peduncles, and posterior columns were found to be especially severe. White matter changes of this type would explain the MR findings in our PPA case 6 (Fig 1), who died at 1.5 months of age.

All 11 published cases of MMA studied after the first year of life had lesions affecting the

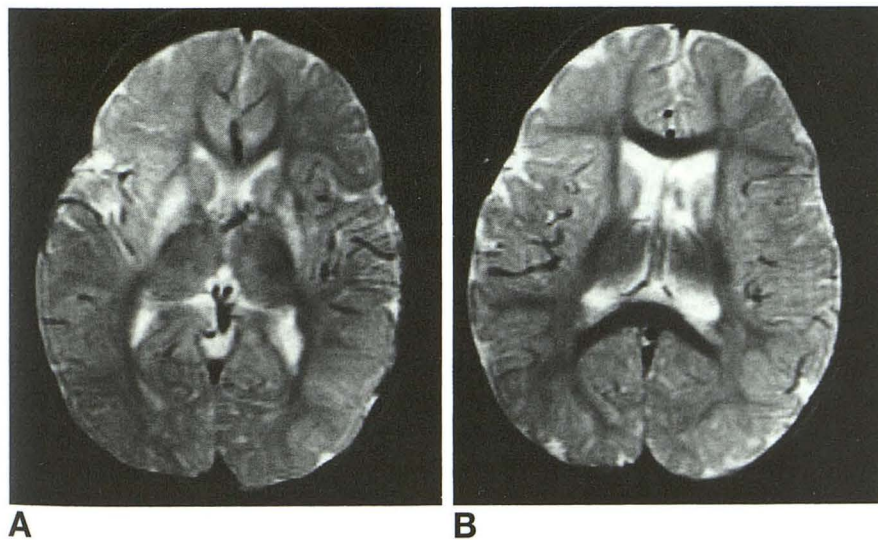


Fig 8. Eighteen-month-old girl with PPA (case 11): muscular hypotonia and severe choreoathetosis.

A and B, MR (T2-weighted) shows slight prominence of sulci and increased intensity within the lentiform nucleus and caudate head bilaterally.

globus pallidus. This need not mirror the true frequency of basal ganglia involvement; many of the cases were probably published because of the unusual lesions in the globus pallidus. In our hospital an MR study of the brain, and often also a CT examination, is part of the routine exam for possible neurometabolic diseases even in patients with minimal or no signs of brain involvement. The frequency of basal ganglia changes in our material therefore should better indicate the true incidence. In a review article on MMA in 1987 the authors stated that "several cases, as yet not fully reported in the literature, have been described to the authors of infarcts in various parts of the brain at several years of age" (14). In all published reports the basal ganglia changes, however, have been limited to globus pallidus and the adjacent parts of the internal capsules.

One report described cerebral atrophy at CT in a 3-year-old girl with PPA known since 2 months of age (2). A retrospective study on the neurologic outcome in PPA identified a total of 20 patients diagnosed during a 25-year period (18). They found the patients were divided into two distinct groups: those with disease onset during the first week of life, and those with onset after the first 6 weeks. The disease was more severe and the prognosis much worse in the early-onset group. CT was performed in 4 children in each group—the patients' exact ages at the CT examinations were not given in the report. In the early-onset group, CT in 3 cases showed cerebral atrophy and in 1 was normal. In 3 of the 4 patients with late-onset PPA, CT showed basal ganglia lesions; in 1 the study was normal. In 1 child the lesion involved the lentiform nuclei; in 1 also the caudate nuclei were affected, and in the third the medial posterior lentiform nucleus, the anterior half of the thalamus, and subcortical white matter were bilaterally involved. In all patients the basal ganglia lesions resolved during 1 to 3 months; in 1 child further basal ganglia lesions later developed. Microscopic examination of the white matter in a 23-month-old infant who died in a metabolic coma secondary to PPA (24) revealed occasional regions of perivascular spongy rarefaction in the caudate nucleus but otherwise well-preserved myelin without spongiform changes.

The reason that the globus pallidus is the most vulnerable ganglia structure in MMA has been discussed in several previous reports (25–

28), but there is no definite explanation. Furthermore, the causes of the apparent difference between MMA and PPA in the distribution of the basal ganglia changes are unknown. It may be caused by specific toxic effects from different metabolites or depend on the fact that different basal ganglia structures might be the metabolically most active structures in the brain in MMA and PPA crises, and therefore are most vulnerable to anoxia and metabolic insults.

In the retrospective series on the outcome of PPA (18), 10 of 11 infants in the early-onset group, with the most severe disease, were of Arab or Indio-Pakistani origin; 8 of 9 in the late-onset group, with milder disease, were European. All our patients are of Saudi Arabian origin, but nonetheless the age at onset and the severity of disease varies markedly. This is in agreement with other reports. A study on a massively inbred Mennonite-Amish community with several patients with PPA, in which the disease in all probability originated from the same ancestor and thus probably was biochemically identical, showed a wide variety of clinical manifestations (21), ranging from severe disease to complete lack of symptoms.

White matter abnormalities and prominent CSF spaces are nonspecific findings, present in many neurometabolic disorders. Basal ganglia lesions are less frequently seen but may occur not only in different organic acidemias but also in anoxic lesions, after methanol intoxication, and also in infectious diseases such as symmetrical basal ganglia changes in herpes simplex encephalitis. The finding of basal ganglia lesions, be they slitlike high-T2 intensity lentiform nuclei, shrunken caudate heads, or acutely swollen basal ganglia, always should prompt examination for possible underlying metabolic disease, so that therapy can be started and thereby, it is hoped, further damage to the brain avoided. If the lesions are limited to the globi pallidi, MMA is the likely cause, but the diagnosis nevertheless has to be confirmed biochemically.

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