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MR Imaging and Proton Spectroscopy in 3-Hydroxy-3-Methylglutaryl Coenzyme A Lyase Deficiency

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Summary: Three patients with 3-hydroxy-3-methylglutaryl coenzyme A lyase deficiency were examined with MR imaging and proton MR spectroscopy. In two patients, both clinically normal, MR images showed a diffuse mild abnormality in signal intensity of the cerebral white matter, with multiple foci of more pronounced signal abnormality superimposed. In the third patient, who was clinically retarded and had a cerebral visual impairment, MR imaging showed, in addition to a diffuse signal abnormality of the cerebral white matter, atrophic scarring of the occipital lobes and abnormal signal intensity of the thalami and basal ganglia. It is highly probable that the additional lesions in the occipital lobes and basal nuclei were related to the episode of severe neonatal hypoglycemia the patient experienced. The MR spectroscopic abnormalities correlated with the degree of disease as evidenced by MR imaging.

Deficiency of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) lyase is an inborn error of leucine degradation and ketone body synthesis (1). The disease is characterized by recurrent episodes of life-threatening metabolic derangement with hypoglycemia, metabolic acidosis, and, often, hyperammonemia, but no ketosis (1, 2). In a considerable proportion of patients the first metabolic crisis occurs in the early neonatal period, and in the majority of patients the first crisis occurs before the age of 9 months. The diagnosis is suggested by abnormalities in urinary organic acids, with increased levels of 3-hydroxyisovaleric acid, 3-methylglutaric acid, 3-methylglutaconic acid, and 3-hydroxy-3-methylglutaric acid (2). Diagnosis is confirmed by demonstration of deficient activity of HMG CoA lyase in leukocytes and cultured fibroblasts. Treatment of acute episodes consists of measures of general support and rapid correction of the hypoglycemia and acidosis (2). Long-term treatment consists of restriction of leucine intake, carnitine medication, and avoidance of fasting (2). With adequate acute and long-term treatment, most children have no remaining damage: they develop normally, with no neurologic abnormalities (3). In a minority of affected children, the episodes of metabolic decompensation lead to serious neurologic damage; in particular, mental retardation (4) or even death (5).

Magnetic resonance (MR) imaging findings have been reported in a small number of patients. They consist mainly of multiple foci of hyperintensity in the cerebral white matter, sometimes accompanied by cerebral atrophy (4, 6, 7).

The purpose of the present study was to evaluate MR imaging and proton MR spectroscopic abnormalities in patients treated for HMG CoA lyase deficiency, to relate the findings to the clinical history and present condition of the patients, and to discuss the results in light of the current literature.

Case Reports

Case 1

A boy was born as the 13th child of remotely consanguineous parents. Five of his siblings had died, of whom three had been proved to have HMG CoA lyase deficiency. In the present patient, the diagnosis of HMG CoA lyase deficiency was established directly after birth, and appropriate treatment was started. He had two episodes of hypoglycemia and lethargy in his third year of life, but his condition was never serious. At present, at the age of 6 years, he is developing normally and has no neurologic abnormalities.

MR imaging, performed at the age of 6 years, revealed a diffuse cerebral white matter hyperintensity on T2-weighted images, with sparing of the U fibers only (Fig 1). The diffuse abnormality in signal intensity was less pronounced on T1-weighted images, on which larger parts of the cerebral white matter had a normal, high signal intensity (Fig 1). In addition, widespread small foci of more severe abnormality in signal intensity were seen within the cerebral white matter on both T1- and T2-weighted images. The corpus callosum was normal. Signal abnormalities were also seen in the posterior limb of the internal capsule, the pontine tegmentum, the hilus of the dentate nucleus, and possibly the dentate nucleus itself. The cerebellar white matter was spared.

Proton MR spectroscopy was performed in a $2 \times 2 \times 2$-cm^3 voxel in the parietooccipital white matter and in a $2 \times 2 \times 2$-cm^3 voxel in the midoccipital area, containing cortex of both hemispheres. Both long- and short-echo-time techniques were used. The point-resolved spectroscopy (PRESS) sequence was used with parameters of 2500/135/128 (repetition time/echo time/excitations). The stimulated-echo acquisition mode (STEAM) sequence was used with 2500/20/128. The averaged measurements were zero filled to 2048 data points, exponentially filtered to give 1 Hz line broadening before fast Fourier transformation. The spectra were quantified by peak area measurements using system software. Ratios of metabolites relative

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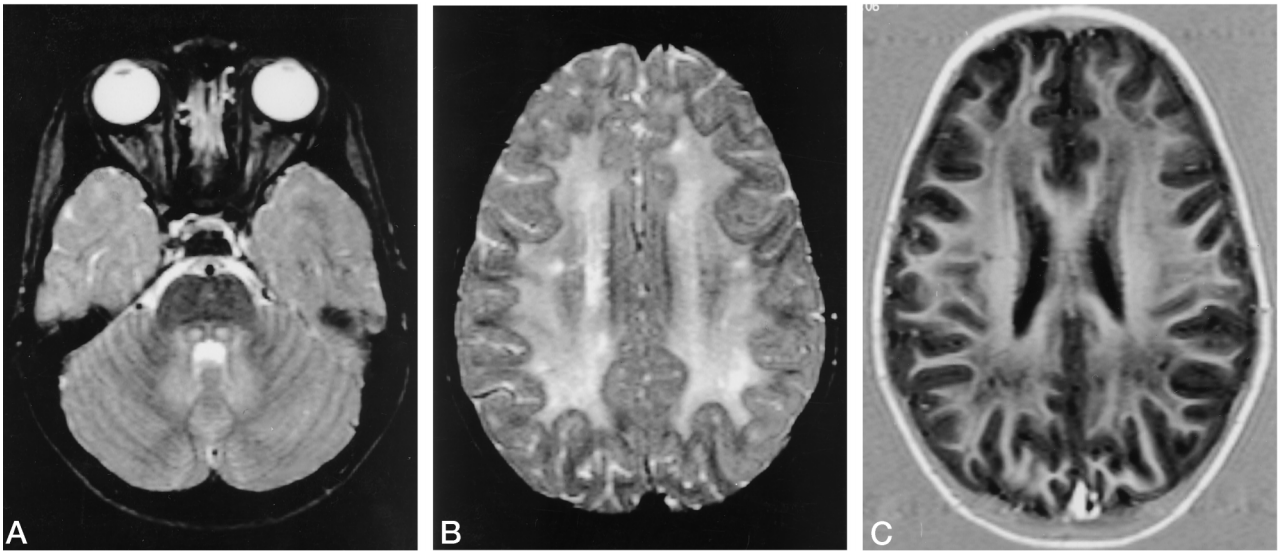


FIG 1. Case 1. Axial T2-weighted (3000/120/1) (*A* and *B*) and T1-weighted (4500/20/1; inversion time, 600) (*C*) MR images show diffuse and multifocal cerebral white matter abnormalities. Two small lesion are seen in the pontine tegmentum (*A*). The hilus of the dentate nucleus and possibly the dentate nucleus itself have a mildly abnormal signal intensity (*A*).

Results of MR spectroscopy

	Age, y	PRESS, 135 Spectra		STEAM, 20 Spectra		*Myo*-inositol/Cr
		NAA/Cr	Ch/Cr	NAA/Cr	Ch/Cr	
Patient						
1 (WM/Co)*	6	1.48/1.59	1.23/1.00	1.24/1.32	1.12/0.82	1.14/0.70
2	10	1.50	1.38	1.23	1.26	1.08
3	4	1.00	0.96	0.86	0.84	0.81
Control subject						
1	3	1.74	0.86	1.51	0.70	0.74
2	8	1.68	0.80	1.48	0.69	0.68
3	12	1.70	0.78	1.42	0.61	0.63
4	17	1.66	0.82	1.50	0.68	0.71

* Separate values for the white matter/cortex (WM/Co) voxel; the rest of the figures refer to white matter voxels.

Note—NAA indicates *N*-acetylaspartate; Cr, creatine; Ch, choline; PRESS, point-resolved spectroscopy; and STEAM, stimulated-echo acquisition mode.

to creatine were calculated and compared with values obtained in control subjects within the same age range. The results are presented in the Table.

Case 2

A girl was born prematurely as the first child of nonconsanguineous parents. The postnatal period was uncomplicated and subsequent psychomotor development was normal. She had a poor appetite, and her diet was low in protein and high in carbohydrates. Asymptomatic HMG CoA lyase deficiency was diagnosed at the age of 6 years, when her sister (case 3) came to medical attention, and appropriate treatment was started. At present, at the age of 10 years, she has no neurologic abnormalities and is doing well in primary school.

MR imaging, performed at the age of 10 years, showed a diffuse, moderate elevation in signal intensity of the cerebral white matter on T2-weighted images (Fig 2A), whereas the signal abnormality was much less evident on T1-weighted images. In addition, small and larger foci of more pronounced signal abnormality were found superimposed on the diffuse signal abnormality (Fig 2A). The U fibers were prominently involved. The corpus callosum was normal. Signal abnormalities were also seen in the posterior limb of the internal capsule, the hilus of the dentate nucleus, and possibly in the dentate nucleus itself. MR spectroscopy was performed in the white matter voxel only. The same techniques were used as described in case 1, and the results are reported in the Table (see also Fig 2B and C).

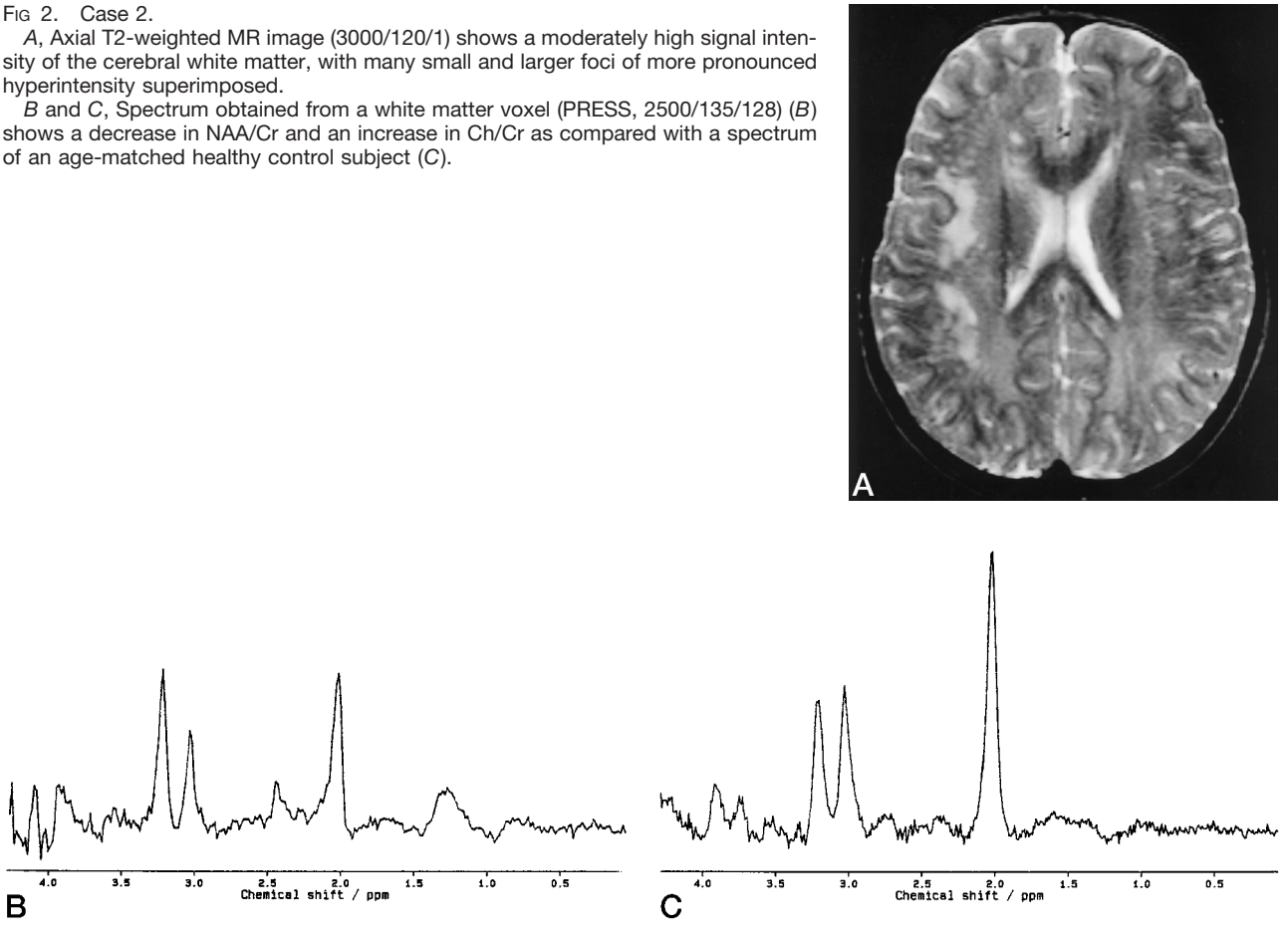
Case 3

A girl was born at term as the third child of the parents of patient 2. From day 2 onward there were increasing feeding difficulties, with vomiting. On day 4 she had an irregular breathing pattern, became increasingly lethargic, and had myoclonic jerks. She was in a coma when admitted to the hospital. Laboratory investigations revealed severe hypoglycemia and a metabolic acidosis without ketosis, which were corrected with intravenous glucose and bicarbonate. Convulsions were treated with phenobarbitone. Computed tomography (CT) of the brain at day 6 showed diffuse hypodensity and some swelling of the cerebral white matter (Fig 3A). In the occipital area, contrast between the cerebral cortex and white matter had disappeared (Fig 3A). A diagnosis of HMG CoA lyase deficiency was established and appropriate treatment was started. A repeat

FIG 2. Case 2.

A, Axial T2-weighted MR image (3000/120/1) shows a moderately high signal intensity of the cerebral white matter, with many small and larger foci of more pronounced hyperintensity superimposed.

B and *C*, Spectrum obtained from a white matter voxel (PRESS, 2500/135/128) (*B*) shows a decrease in NAA/Cr and an increase in Ch/Cr as compared with a spectrum of an age-matched healthy control subject (*C*).



CT study at the age of 2 months showed severe cystic degeneration of the occipital and parietooccipital white matter (Fig 3B). The frontal and temporal white matter was mildly hypodense, but not cystic. After the neonatal period, the child was admitted repeatedly to the hospital because of intercurrent illnesses with feeding difficulties, fever, and often epileptic seizures; but with adequate care she never again experienced hypoglycemia. At present, at the age of 4 years, she is microcephalic and severely retarded, and there is evidence of cerebral visual impairment.

MR imaging was performed at the age of 4 years. T2-weighted images showed diffusely abnormal signal intensity of the cerebral white matter, which was much less apparent on the T1-weighted images (Fig 3C–E). The parietooccipital areas, including the cortex and white matter, were atrophic and had very high signal intensity on T2-weighted images and very low intensity on T1-weighted images. On T2-weighted images, the globus pallidus and the dorsolateral part of the thalamus had a high signal intensity; parts of the putamen and caudate nucleus had a mildly elevated signal intensity. Bilaterally, areas of high signal intensity were seen in the pontine tegmentum, the hilus of the dentate nucleus, and possibly the dentate nucleus itself. The corpus callosum, internal capsule, and cerebellar white matter were spared. MR spectroscopy was performed in a white matter voxel. The same techniques were used as described in case 1, and the results are reported in the Table.

Discussion

A few articles have reported the CT findings during acute metabolic crises in HMG CoA lyase deficiency (8–10). CT scans reportedly showed white matter hypodensity and swelling (8–10), similar to our findings in case 3. Microscopic examination of brain tissue, obtained during an acute metabolic crisis by brain biopsy (8) or autopsy (5), showed spongiform degenerative white matter changes and gliosis.

Articles on MR imaging in HMG CoA lyase deficiency (4, 6, 7) document the findings in treated patients who were metabolically stable. Similar to the MR imaging findings in our patients, multiple abnormal white matter foci were observed within the cerebral white matter, varying in number from a few to, more often, a multitude of lesions, and varying in size from very small (a few millimeters) to larger and more confluent lesions. In our patients and in the patients reported by Ferris et al (6), the small white matter foci were found on a background of slight to mild signal abnormality of almost the entire cerebral white matter. In case 3, the diffuse signal change was more pronounced, so that foci of abnormal signal intensity, if present, may not have been visible. The combination of diffuse mild and multifocal more serious cerebral white matter abnormalities on MR images is unique (11).

The pathogenesis and histopathologic basis of both the diffuse mild white matter changes and the multifocal more pronounced white matter abnormalities are not known. There is a striking, consistent discrepancy between the extensive white matter abnormalities on MR images and the lack of clinical findings in the patients reported so far. Most patients are clinically normal (4, 6) or have an intelligence just below average (7). This observation excludes progressive demyelination as a histopathologic basis. Hypomyelination and gliosis, as observed in other metabolic disorders, may be factors contributing to the white matter signal abnormality.

In case 3, MR images showed several additional abnormalities, until now not reported in HMG CoA lyase deficiency: changes in signal intensity in the thalami and basal ganglia, and a combination of signal change and atrophy in the occipital

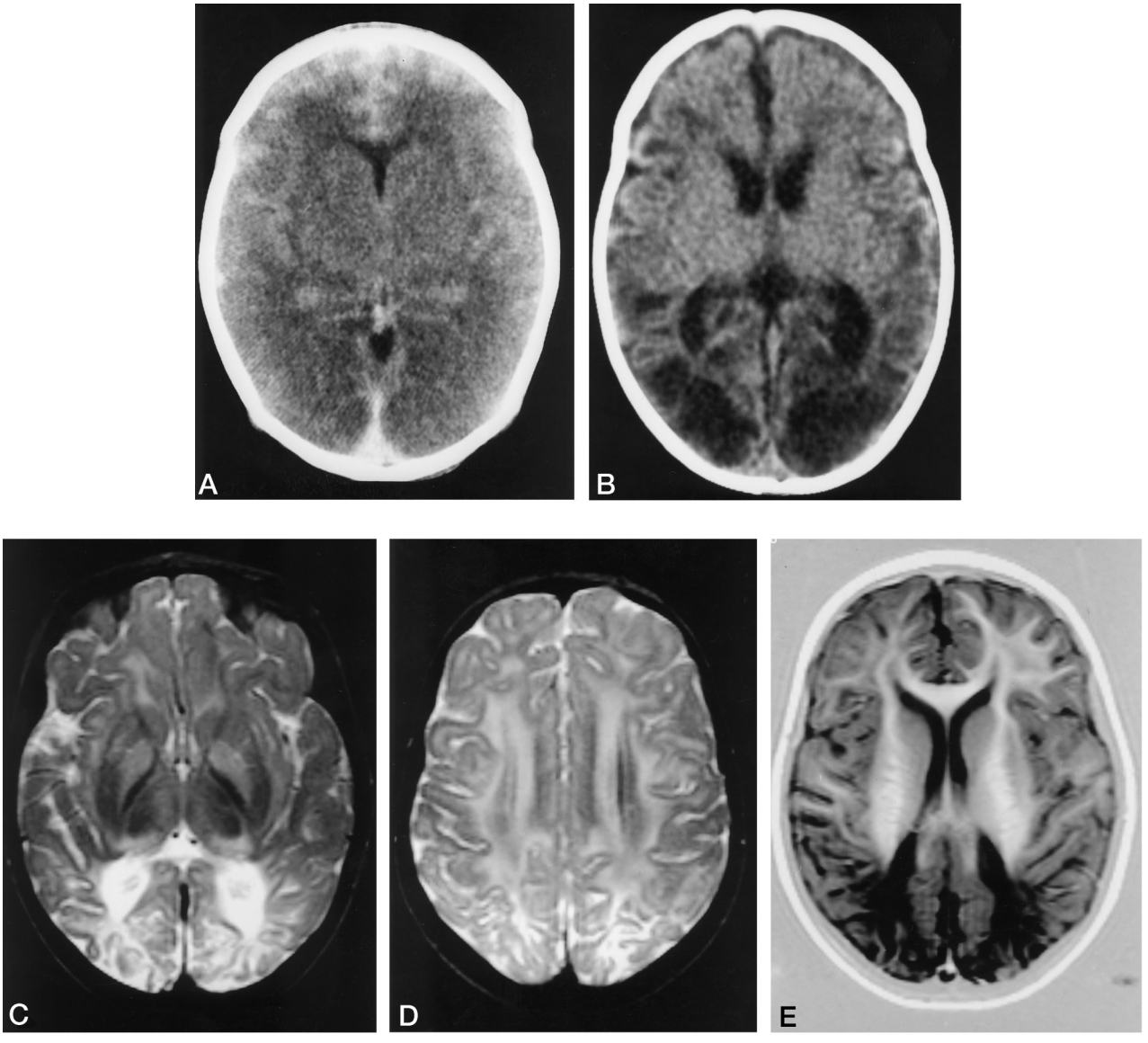


FIG 3. Case 3.

A, CT scan of the brain during a neonatal episode of metabolic decompensation shows diffuse hypodensity and swelling of the white matter and loss of contrast between the cortex and white matter in the occipital area.

B, Two months later, extensive cystic degeneration is seen in the occipital area.

C–E, On follow-up, transverse T2-weighted MR images (3000/120/1) (*C* and *D*) show a diffuse signal abnormality of the cerebral white matter, whereas the signal intensity is close to normal on a T1-weighted image (4500/20/1; inversion time, 600) (*E*). The occipital area is atrophic and has a highly abnormal signal intensity on both T1- and T2-weighted images. There are signal abnormalities in the thalamus and globus pallidus, and to a lesser extent in the putamen and caudate nucleus (*C*).

area with extension to the parietal and temporal areas (Fig 3). This is the only patient reported so far who has both extensive MR imaging abnormalities and serious neurologic sequelae. It is known that a minority of patients with HMG CoA lyase deficiency who have survived metabolic crises have remaining deficits, such as developmental delay, microcephaly, and spasticity (1–4). The patient reported in our case 3 suffered a life-threatening metabolic decompensation with serious hypoglycemia in the neonatal period, and the CT scans showed that the occipital lesions arose during that time (Fig 3). It is known that in cases of neonatal hypoglycemia, the occipital lobes are most vulnerable and that the basal ganglia may also be involved, although to a lesser extent (12, 13). The occipital lobe damage may lead to cerebral visual disturbances (12). Hypoglycemia at other ages leads to a more diffuse involvement of the cortex (14). So, it is highly probable that the neonatal hypoglycemia caused the occipital and basal nuclei abnormalities in patient 3.

MR spectra of the white matter showed similar changes in the three patients, although to a different degree. *N*-acetylaspartate (NAA)/creatine (Cr) was moderately decreased in patients 1 and 2, and more severely decreased in patient 3. Choline (Ch)/Cr and *myo*-inositol/Cr were more severely increased in patients 1 and 2 than in patient 3, in whom these ratios were only slightly increased. The higher NAA/Cr in patients 1 and 2 relative to patient 3 would be compatible with a better preservation of axons and neurons (15), which is in agreement with the less severe MR imaging abnormalities and clinical picture of patients 1 and 2. However, as far as can be judged from Ch/Cr and *myo*-inositol/Cr levels (16, 17), white matter abnormalities were more "active" in patients 1 and 2, with enhanced membrane turnover (16) and gliosis (17), respectively. An important factor in this respect may be

that the white matter voxel in patient 3 contained, in large part, the atrophic remnants of the occipital lobe.

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