Neuroradiology (1997) 39: 546–550

H. Maeda
M. Sato
A. Yoshikawa
M. Kimura
T. Sonomura
M. Terada
K. Kishi

Brain MR imaging in patients with hepatic cirrhosis: relationship between high intensity signal in basal ganglia on T_1-weighted images and elemental concentrations in brain

Received: 12 August 1996
Accepted: 17 December 1996

H. Maeda (✉) · M. Sato · A. Yoshikawa · M. Kimura · T. Sonomura · M. Terada · K. Kishi
Department of Radiology,
Wakayama Medical College,
27-7, Wakayama City, 640, Japan

Abstract In patients with hepatic cirrhosis, the globus pallidus and putamen show high intensity on T1-weighted MRI. While the causes of this high signal have been thought to include paramagnetic substances, especially manganese, no evidence for this has been presented. Autopsy in four cases of hepatic cirrhosis permitted measurement of metal concentrations in brain and histopathological examination. In three cases the globus pallidus showed high intensity on T1-weighted images. Mean manganese concentrations in globus pallidus, putamen and frontal white matter were 3.03 ± 0.38, 2.12 ± 0.37, and 1.38 ± 0.24 (μg/g wet weight), respectively, being approximately four- to almost ten-fold the normal values. Copper concentrations in globus pallidus and putamen were also high, 50 % more than normal. Calcium, iron, zinc and magnesium concentrations were all normal. The fourth case showed no abnormal intensity in the basal ganglia and brain metal concentrations were all normal. Histopathologically, cases with showing high signal remarkable atrophy, necrosis, and deciduation of nerve cells and proliferation of glial cells and microglia in globus pallidus. These findings were similar to those in chronic manganese poisoning. On T1-weighted images, copper deposition shows no abnormal intensity. It is therefore inferred that deposition of highly concentrations of manganese may caused high signal on T1-weighted images and nerve cell death in the globus pallidus.

Key words Brain magnetic resonance imaging · Basal ganglia · Cirrhosis, hepatic · Manganese

Introduction

Changes in the brain of patients with hepatic cirrhosis include atrophy [1], and high signal in the globus pallidus and putamen on T1-weighted MRI [2–5]. Inoue et al. [2] reported high signal in patients with collateral vessels more than 10 mm in diameter originating from the superior mesenteric vein [2]. While it is generally accepted that portal-systemic encephalopathy is accompanied by chronic neuropsychiatric disturbances and associated with irreversible brain damage [6], it is not known if there is an association between high signal on MRI and psychosis.

The high signal is reported to extend, as the liver dysfunction is exacerbated, from the globus pallidus, putamen, internal capsule, hypothalamus and tegmentum of the midbrain to the white matter [3]. Although the possible causes of the high signal on T1-weighted images are generally considered to include deposition of paramagnetic substances, lipids, calcification, melanin and methaemoglobin, no confirmatory evidence has been presented. We carried out autopsies on four cases of hepatic cirrhosis and obtained useful information about histopathological findings and metal concentrations in the brain.

Subjects and methods

The subjects were four men, average age 58.8 years, with hepatic cirrhosis due to hepatitis C virus. At the time of MRI, one was in Child's grade A and three in grade C. All had hepatocellular carcinoma, and one an old left putaminal haemorrhage; the cause of death was hepatic failure in each case. Although no patient showed definite encephalopathy, insomnia and a labile affect were observed in two.

MRI was performed with 1.5-T or 0.5-T superconducting systems on which axial and coronal spin-echo images were obtained with T1-weighting (repetition time / echo time / number of excitations, 500/15–20 ms/2–3) and T2-weighting (2500–3000/80–100/1); slice thickness was 8 mm with a 2 mm gap, matrix 192 × 256 and field of view 20 cm. Imaging was performed 5–13 months before death.

Autopsy was conducted 3–9 h after death. The brain was divided into two hemispheres with a stainless steel knife, and one of the hemispheres was fixed in formalin. The globus pallidus, putamen and frontal white matter of the other hemisphere were resected, placed in a polyvinyl package and stored at –80 °C until analysis.

Metals including manganese (Mn), copper (Cu), calcium (Ca), iron (Fe), zinc (Zn) and magnesium (Mg) were analysed; their contents were measured using inductively-coupled atomic-emission spectrometry (ICP-AES). The wet weight of each specimens was measured. Concentrated sulphuric acid 2.0 ml was added to the specimens and, using a sand bath, they were subjected to hydrolysis at 100–130 °C until the residual liquid had a volume of 0.3 ml. When the residue was brown or black, concentrated sulphuric acid was added stepwise, in 1-ml increments, to repeat hydrolysis until the liquid became colourless or pale yellow. Water was added to this residue to make 20 ml, and the liquid so obtained was filtered with a 0.8-mm membrane filter; the filtrate was used for testing. Five aliquots of 2.0 ml concentrated sulphuric acid were subjected to a similar procedure; the solution obtained was used as the control. Each solution was subjected to ICP emission spectrochemical analysis. Emission intensity was measured for each element and, using the appropriate calibration curve prepared using an atomic absorption reference solution, the content of the specimen was calculated. The results were then corrected using the values from the control and the actual content of the metal elements in the specimen was calculated.

For histological investigation, specimens of the globus pallidus, putamen and frontal white matter from three cases with no left putaminal haemorrhage were stained with haematoxylin-eosin (H & E) and Kluver-Barrera (KB) stains, 10–14 days after formalin fixation.

Results

The three cases in Child's grade C (Table 1, cases 1–3), showed no abnormal signal on T2-weighted images, but remarkably high signal was detected from the globus pallidus, putamen and internal capsules bilaterally and from the hypothalamus to the tegmentum of the midbrain on T1-weighted imaging (Fig. 1). Case 4, with a left putaminal haemorrhage, belonged to Child's grade A (Table 1). MRI showed no abnormal signal in the right cerebral hemisphere on T1- or T2-weighted images; this was therefore used as the control.

The presence or absence of high signal on T1-weighted images and the cerebral metal concentrations are shown in Table 1. In the cases with high signal in the globus pallidus, mean manganese concentrations in the globus pallidus, putamen and frontal white matter were high: 3.03 ± 0.38, 2.12 ± 0.37 and 1.38 ± 0.24 (μg/g wet weight), respectively. The concentrations in the case showing no high signal were lower: 0.42, 0.47 and 0.40 (μg/g wet weight), respectively.

Table 1 High signal intensity of globus pallidus on T1-weighted images and metal concentrations (μg/g wet weight) in the globus pallidus, putamen, and white matter in cirrhosis

Element	Case	High signal on T1-weighted images	Globus pallidus	Putamen	White matter
Mn	1	+	3.00	2.27	1.17
	2	+	2.59	1.62	1.25
	3	+	3.51	2.48	1.72
	4	–	0.42	0.47	0.40
Cu	1	+	8.28	8.63	6.06
	2	+	14.11	15.98	6.60
	3	+	17.21	24.21	8.77
	4	–	4.71	4.73	5.30
Ca	1	+	67.94	58.60	55.70
	2	+	64.72	59.82	60.47
	3	+	178.05	114.01	66.37
	4	–	103.72	74.26	97.80
Fe	1	+	172.70	183.80	60.70
	2	+	241.63	194.55	31.75
	3	+	147.36	139.69	50.63
	4	–	63.30	63.30	48.80
Zn	1	+	13.35	16.05	11.00
	2	+	20.41	20.22	9.53
	3	+	19.42	22.06	8.13
	4	–	18.46	14.52	10.11
Mg	1	+	114.80	126.30	124.00
	2	+	155.48	163.09	145.34
	3	+	178.43	201.77	162.38
	4	–	161.90	149.70	158.90

In the cases with high signal, mean copper concentrations in the globus pallidus, putamen and white matter were 13.20 ± 3.70, 16.27 ± 6.36 and 7.14 ± 1.17 (μg/g wet weight), respectively; they were high in the globus pallidus and putamen. In the other case the values were 4.71, 4.73 and 5.30 (μg/g wet weight), respectively, all low. In the first three cases mean iron concentrations were 187.2 ± 39.8, 172.7 ± 23.7, and 47.7 ± 12.0 (μg/g wet weight), all higher than the concentrations in the last case (63.3, 63.3 and 48.8 μg/g wet weight). No differences were found in the calcium, zinc or magnesium concentrations, irrespective of the presence or absence of high signal.

Histologically, the cases showing high signal showed remarkable atrophy, necrosis and deciduation of the nerve cells of the globus pallidus, with reactive glia and microglia (Fig. 2). Similar changes, of medium severity, were observed in the putamen. Nerve cells in the cerebral white matter had undergone slight denaturation.

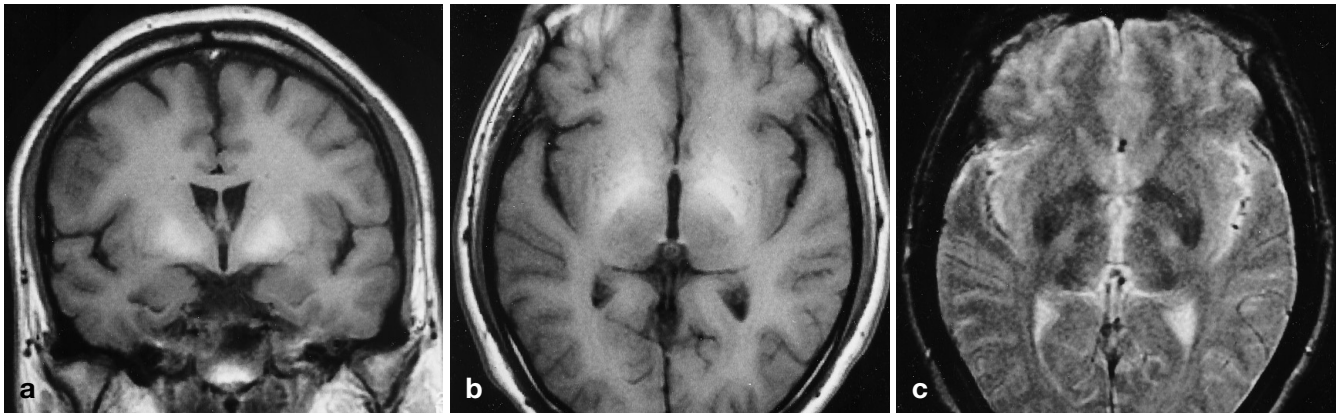

Fig. 1 a–c A 60-year old man with liver cirrhosis. **a, b** T1-weighted images (500/15) show high signal in globus pallidus and putamen. **c** T2-weighted image (2500/80) shows no abnormal intensity

Discussion

In patients with hepatic cirrhosis, the globus pallidus and putamen come to show bilaterally symmetrical high signal on T1-weighted images as hepatic function deteriorates, while no abnormality is seen on T2-weighted imaging or CT. Calcification and haemorrhage are effectively excluded. The causes of the high signal include paramagnetic substances, especially manganese, which escapes hepatic clearance because of a portal-systemic shunt or liver dysfunction [3, 7]. However, this has not been confirmed to date.

Table 2 shows the normal concentrations of metals in the brain [8–15]. We found normal manganese concentrations in a case with no high signal, in the globus pallidus, putamen and white matter, while, in the presence high signal, the mean manganese concentrations in these structures were increased to approximately 4.5- to 9.5-fold, 4- to 5.5-fold and 5- to 7.5-fold, respectively. Copper concentrations in the globus pallidus and putamen in the cases exhibiting high signal were approximately 1.5-fold the normal. Although iron also was more highly concentrated in the globus pallidus and putamen in these cases than in the other case, the levels were still normal. Calcium, iron, zinc, and magnesium contents were all normal.

Thus, the white matter contained a large amount of manganese, while the globus pallidus and putamen also contained large amounts of copper. Copper deposition, as in Wilson's disease, causes remarkably low signal on

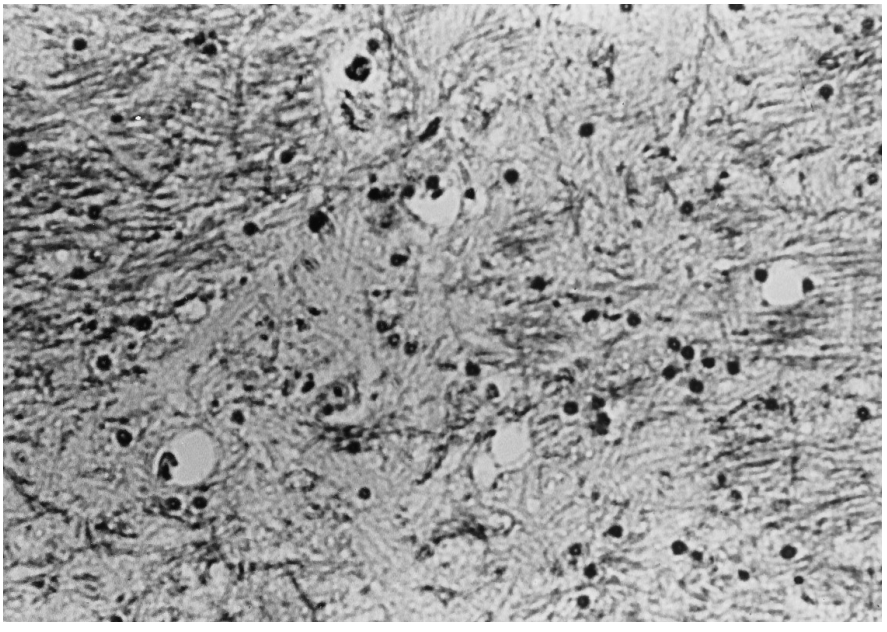

Fig. 2 The globus pallidus in a patient with hepatic cirrhosis shows a marked loss of the nerve cells with proliferation of the glia and microglia. Kluver-Barrera stain; original magnification × 200

Table 2 Mean metal concentrations of human brain in the literature (μg/g wet weight). Dry-weight values were converted to wet weight using freeze-dried to wet-weight ratios: whole brain 0.211 [15]; globus pallidus 0.230 [16]; putamen 0.203 [16]; white matter 0.276 [16]

Element	Whole brain	Globus pallidus	Putamen	White matter
Mn	0.32–0.74 [8] 0.30–0.51 [9]	0.32 [10] 0.382 [11]	0.39 [10] 0.518 [11]	0.31 [12] 0.184 [11]
Cu	2.89–8.03 [9]	8.05 [13] 7.68 [10]	8.93 [13] 9.58 [10]	
Ca	109.2–147.7 [9]	54.4 [10] 131.3 [14]	60.2 [11] 124.0 [14]	
Fe	35.6–54.2 [9]	160.4 [13] 178.5 [10]	118.9 [13] 123.4 [10]	77.0 [14]
Zn	10.3–17.2 [9]	15.9 [13]	15.2 [13]	15.6 [14]
Mg	92.8–140.3 [9]	144.0 [13]	150.0 [13]	

T2-weighted images, while T1-weighted images are reported to be normal [16]. On the other hand, manganese is a paramagnetic substance which strongly shortens T1 relaxation time, and this property is reported to be dose-dependent [17]. It is therefore, inferred that deposition of manganese in high concentration may cause high signal in not only in the globus pallidus and putamen but also the cerebral white matter.

Usually, 1–3.5 % of orally ingested manganese is absorbed into the blood [18, 19], 98 % of which is cleared in the liver and excreted in the bile [20]. The blood manganese, after binding with blood transferrin and through the action of endocytosis via transferrin receptors, is transferred to brain through the blood-brain barrier [21]. In adults, irrespective of age, there is no difference in the amount of manganese in the brain, presumably because of a homeostatic mechanism regulating its level [11]. However, manganese parenterally administered, for instance in patients undergoing long-term total parenteral nutrition [22] or in employees of a manganese ore crushing plant [23], is reportedly deposited in the brain, especially the globus pallidus. In hepatic cirrhosis, manganese clearance in the liver is reduced due to portal-systemic shunts or liver dysfunction. Since blood manganese concentration in patients with cirrhosis is higher than in normal humans [24], manganese is probably deposited in the brain.

Autopsy findings in a patient with chronic manganese poisoning included atrophy and deciduation of the globus pallidus, especially the medial segment, an moderate increase in the number of astrocytes, and proliferation of glial fibres, coupled a with reduced number of nerve cells in the putamen and caudate nucleus [25]. The findings in our cases were similar. However, the manganese content in the brain in chronic manganese poisoning was reportedly normal; because manganese had been reduced due to therapy with intravenous edetic acid, which promotes manganese excretion, and oral *L*-dopa. We infer that, even if the excess manganese in the brain was excreted, the affected nerve cells remained the same because of irreversible damage.

The early symptoms in patients with chronic manganese poisoning are nonspecific, including asthenia, anorexia, irritability, insomnia, uncontrolled violence and labile affect. As intoxication progress, parkinsonism, with inappropriate laughing, bradykinesia, speech disorder, mask-like face and tremor, becomes manifest [26–28]. In such cases, however, pathological change in the substantia nigra, as seen in parkinsonism, is not observed; changes in basal ganglia, including the globus pallidus, are thought to be associated with extrapyramidal signs [25]. The picture is similar in cirrhosis. According to Read et al. [29], parkinsonism was found in 5 of 21 patients with cirrhosis. We saw neuropsychological disturbance (insomnia, labile affect) in two of four cases, maybe because of manganese deposition and accompanying nerve cell atrophy or deciduation.

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BOOK REVIEW

Posterior Circulation Disease. Ed.: Louis R. Caplan. Blackwell Science Ltd, 1996. (ISBN 0-86542-298-2) hardcover, £ 95.00

This monograph to the subject of posterior circulation vascular disease contains more than 700 pages. It represents the major life's work of the most distinguished worker and pioneer in this field. The book defines the current level of understanding of posterior circulation disease. Moreover, the volume integrates personal clinical experience and the observations of others in a unique and clear manner.

The book is divided into three parts, 'General features of vascular disease in the posterior circulation', 'Posterior circulation ischemia' and 'Hemorrhagic posterior circulation stroke'. The first part deals with anatomy, pathology, signs and symptoms, diagnostic modalities and treatment. The second discusses posterior circulation ischaemia primarily with regard to the location of vascular lesions and refers to the experience of the New England Medical Center Posterior Circulation Registry. These two parts provide a large amount of information which overlaps to some degree. Each chapter of the second part is formatted in a similar fashion: background and development of ideas, pathology, symptoms and signs, treatment, conclusions. Treatment recommendations are well balanced. In particular, different treatment strategies are discussed critically and in detail. The third part includes the underlying aetiology of parenchymatous and subarachnoid haemorrhage in the posterior circulation.

The index and references are comprehensive; the references, placed at the end of each chapter, are up-to-date. The drawings and diagrams are of uniformly high quality and carefully selected. Unfortunately some neuroradiological illustrations (angiograms, CT, MRI) are of lesser quality, and several images are upside-down. Overall the book reads well and provides a comprehensive review of this field.

In my opinion, this book is useful not only to neurologists but also to clinical neuroradiologists who wish to extend their knowledge and gain a better understanding of the neurological background in posterior circulation ischaemia. This book should find its way into neuroradiological libraries, as it will remain a standard reference text in the future.

A. Thron, Aachen