

Type II (adult onset) citrullinaemia: clinical pictures and the therapeutic effect of liver transplantation

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Abstract

Objective—Adult onset type II citrullinaemia is an inherited disorder of amino acid metabolism caused by a deficiency of liver specific argininosuccinate synthetase activity. Most of the patients with this disease were reported in Japan and therefore, this disease has not been well recognised outside this country. The detailed clinical pictures of the patients with type II citrullinaemia are reported and their outcomes after liver transplantation referred to.

Methods—Ten patients with this disease were evaluated. Seven of them underwent liver transplants using a graft obtained from a healthy family member.

Results—There were six men and four women; the age of onset of encephalopathy ranged from 17 to 51 years. The initial symptom in nine patients was sudden onset disturbance of consciousness, and one patient had long been regarded as having a chronic progressive psychotic illness. High concentrations of plasma citrulline and ammonia were commonly seen on admission. Although brain CT or MRI lacked any consistent findings, the EEG was abnormal in all patients, showing diffuse slow waves. Additionally, in five patients chronic pancreatitis preceded the onset of encephalopathy. After liver transplantation the metabolic abnormalities, including abnormal plasma concentrations of citrulline and ammonia, were immediately corrected and all neuropsychic symptoms soon disappeared, except for impaired cognitive function in one patient. Six out of these seven patients returned to their previous social lives, including work.

Conclusions—The clinical concept of adult onset type II citrullinaemia coincides well with the range of hepatic encephalopathy, and liver transplantation is a very promising therapeutic approach. (*J Neurol Neurosurg Psychiatry* 2001;71:663-670)

Keywords: citrullinaemia; urea cycle disorder; hepatic encephalopathy; liver transplantation

five urea cycle enzymes mainly located in the liver.¹ This disorder can be classified into three types²: neonatal/infantile (types I and III) and adult (type II). Classic types I and III citrullinaemia (the neonatal/infantile forms: CTLN1) are known to be caused by mutations of the ASS gene,^{3,4} whereas in patients with type II citrullinaemia (CTLN2) no primary defect has been found within the ASS gene locus.⁵ Recently, however, the causative gene of type II citrullinaemia was identified as the “citrin gene” (SLC25A13).^{6,7} Patients with type II citrullinaemia display various neurological manifestations closely resembling those of hepatic encephalopathy. In the past, most patients usually followed rapidly deteriorating clinical courses and died of severe brain oedema within a few years of onset,⁸ but some patients with this disease have recently been treated with liver transplantation.⁸⁻¹²

In this report we describe the clinical pictures of 10 patients with the disease, including the therapeutic effects of liver transplantation.

Patients and methods

From 1990 to 2000, 10 patients (six men and four women) with type II citrullinaemia were examined. They were diagnosed according to criteria described previously¹³: high concentrations of plasma citrulline and ammonia, a slight increase in plasma concentration of arginine, and a marked decrease in hepatic ASS activity with normal kinetic properties (table 1). All the patients were shown to be homozygous or compound heterozygous for mutations of the citrin gene, as already reported elsewhere.^{6,7} On admission the EEG, CT, and MRI examinations were routinely performed and additionally, six patients who were available had brain single photon emission computed tomography (SPECT) using ¹²³I-IMP.

Seven of the 10 underwent liver transplantation. In Japan, full liver transplantation from cadaveric donors is uncommon because brain death is not yet widely recognised as a definition of death, and as an alternative we performed liver transplantation using grafts from living donors, consisting of patients’ fathers, mothers, or siblings, all of whom were shown to have normal plasma concentrations of citrulline and ammonia and also to have well preserved urea cycle enzymatic activity in biopsied liver tissue. The details of the operative technique have been reported elsewhere.^{14,15} Briefly, during the operation, the

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Citrullinaemia is a rare hereditary metabolic disorder characterised by highly increased concentrations of citrulline and ammonia in the plasma, which is ascribed to a deficiency of argininosuccinate synthetase (ASS), one of the

Table 1 Clinical summary and laboratory data

Patient	Age at onset	Sex	Duration of illness preop/postop (months)	CT/MRI	SPECT	ASS activity in liver (U/mg protein)	Plasma (on admission)			Serum PSTI (ng/ml)	(*After transplantation)		
							Citrulline (nmol/ml)	Ammonia (μ g/dl)	Arginine (nmol/ml)		Citrulline (nmol/ml)	Ammonia (μ g/dl)	Arginine (nmol/ml)
1	24	Male	7	N	—	0.0039	571.0	317	297.9	—	—	—	
2	25	Male	43	N	N	0.0030	794.6	137	119.7	14.0	—	—	
3	12	Female	118/29	A	A	0.0068	174.9	685	128.3	120.0	37.4	64	113.4
4	51	Female	8/6	A	A	0.00032	668.5	520	242.2	21.0	28.6	34	60.9
5	29	Male	21	N	A	0.00167	1500.6	118	1589.0	13.0	—	—	—
6	24	Male	7/65	N	—	0.0018	782.2	165	279.1	123.2	55.1	50.0	124.6
7	44	Male	11/50	N	—	0.0044	167.4	172	154.4	260.0	36.8	34.0	102.9
8	23	Female	7/32	N	—	0.0012	207.5	213	111.5	—	28.5	30	144.0
9	17	Female	5/26	A	A	0.0013	498.1	201	199.6	29.0	34.6	103	70.8
10	20	Male	144/13	A	A	0.00103	404.2	91	166.9	35.0	54.0	74	105.9

N=Normal; A=abnormal; —=not examined.

The following urea cycle enzyme activities were assayed using the biopsied liver tissue: carbamylphosphate synthetase, ornithine transcarbamylase, argininosuccinate synthetase (ASS), argininosuccinate lyase, arginase, and except ASS all other enzyme activities were normal in these 10 patients.

Normal values: ASS 0.033 \pm 0.012 U/mg protein, citrulline: 10.8–36.5 nmol/ml, ammonia: <41 μ g/dl, arginine: 39.6–138.4 nmol/ml, PSTI: 4.6–12.2 ng/ml.

patient's whole liver was removed. The left lobe was harvested from the living donor and transplanted orthotopically.

The postoperative follow up for the patients ranged from 6 to 65 months. During this period, neurological examination, routine laboratory tests including measurement of plasma concentrations of amino acids and ammonia, EEG, and brain MRI were regularly carried out. Brain SPECT was also performed on five of these seven patients.

Results

CASE REPORTS

Patient 1

The patient was a 25 year old businessman. He suddenly went into a delirious state in February 1990 and was admitted to hospital; he showed violent flapping tremor and very high concentrations of plasma ammonia (317 μ g/dl) and citrulline (571.0 nmol/ml). Intravenous infusion of arginine and branched amino acids was started, and he was given a low protein diet (protein content 40 g/day). However, in the subsequent 5 months a delirious state with abnormal behaviour recurred five times. At the end of July he was transferred to our hospital.

He was 182 cm tall and weighed 54 kg. He was alert, and neurological examinations were normal. Although routine laboratory data (including electrolytes, liver, and renal function tests) were unremarkable, the plasma concentrations of ammonia and citrulline were still high. He was scheduled to receive preoperative examinations, but during the next 2 weeks disorientation and emotional lability repeatedly appeared despite intensive therapy with intravenous infusion of arginine and branched amino acids, and oral administration of lactulose (60 ml/day). The plasma concentration of ammonia gradually increased, finally reaching 820 μ g/dl, and the patient fell into a deep coma. Plasma exchange and peritoneal dialyses were repeated several times, but the encephalopathy did not improve (fig 1). At the end of September he died. The duration of illness was 7 months.

Patient 2

The patient was a 25 year old cook. He had been abnormally fond of peanuts since childhood. He had a history of chronic pancreatitis

and at the age of 16 underwent pancreaticojejunostomy to relieve this disorder. One night in April 1997 he suddenly woke up, shrieked, and started banging his head violently against the wall. The next morning he was normal. He experienced a similar attack one month later: he suddenly attacked his friends without any reason and at that time looked extremely excited. He was taken to a local hospital where highly increased plasma concentrations of ammonia (137 μ g/dl) and citrulline (794.6 nmol/ml) were detected.

At examination, he was 162 cm tall and weighed 53 kg. He was alert and neurological findings were normal. Intravenous infusion of arginine and branched amino acids was started, with restriction of oral protein intake (40 g/day), and oral administration of lactulose (90 ml/day) and kanamycin (1.5 g/day) was added. Plasma concentrations of ammonia and citrulline decreased but remained abnormally high. During his stay in hospital he sometimes fell into a delirious state, accompanied by a flapping tremor, but these episodes were usually relieved within 2 or 3 days by stopping oral intake of food. He did not want to undergo liver transplantation. Since discharge he has been receiving intravenous infusions of arginine and branched amino acids every day at the outpatient department and taking the same medicines. In the past 3 years he has had six attacks of disturbed consciousness, all of which have led to admission to hospital for a few days, and he remains unemployed.

Patient 3

This patient was 21 years old when she visited us. She had been very fond of soybean products since childhood. After entering junior high school she often complained of severe headache, appetite loss, and insomnia. She was first diagnosed as having depression at the age of 15, but auditory and visual hallucinations and catatonic behaviour appeared and diagnosis was changed to schizophrenia. From the age of 18 she often experienced syncopal attacks and also showed abnormal behaviour including destroying utensils and injuring herself. The alternating appearance of severe anorexia and excessive eating further worsened her condition. In January 1998 (at the age of 21) she was admitted to another hospital because of

prolonged loss of consciousness. High concentrations of plasma ammonia (685 $\mu\text{g/dl}$) and citrulline (174.9 nmol/ml) were detected.

At examination she was 171 cm tall, weighed 46 kg, and laboratory data showed a moderately increased serum concentration of triglyceride (374 mg/dl , normal: <150 mg/dl). She received a liver transplant using a graft obtained from her father, aged 50. After operation her neuropsychological condition changed dramatically: her severely depressive and catatonic mood disappeared and she became very cooperative, with frequent smiling. Syncope did not recur and her mental ability rapidly improved (her score on the Japanese Wechsler adult intelligence scale-revised was 40 on admission and 79 at 3 months after the operation (normal around 80)). Since discharge she has been helping her mother with housework.

Patient 4

The patient was a 52 year old woman on referral. In August 1999, she noticed severe general fatigue and transient dysarthria; a few days later she was found in a comatose state with generalised tonic-clonic convulsion at her home and was admitted to a local hospital. Her disturbed consciousness continued for several days, and then improved. Because a high concentration of plasma ammonia (520 $\mu\text{g/day}$) was detected sodium benzoate (7.5 g/day) was given. After discharge the plasma concentration of ammonia remained high (300–400 $\mu\text{g/dl}$) and her mental state gradually deteriorated with intermittent appearance of violent hand tremor. In January 2000 she was

readmitted to hospital because of a severe apathetic state and MRI showed an extensive cerebral white matter lesion (fig 2). She was switched to hyperalimentation with branched amino acids and her consciousness improved.

At examination in April 2000, she was 152.5 cm tall and weighed 48 kg. Neurological examination showed normal somatic motor and sensory functions, but cognitive functions were seriously disturbed: she had recent memory loss and transcortical sensory aphasia, the second being predominant. Evaluation using the Japanese Wechsler adult intelligence scale-revised was impossible, and instead she was given the mini mental state examination, achieving a score of 11/30. In May she received a liver transplant using a graft obtained from her younger brother, aged 46. After the operation her cognitive function remained unchanged, but she has been managing without much help since discharge.

CLINICAL SUMMARY OF THE REMAINING SIX PATIENTS

Patient 5

This 30 year old male patient experienced the first episode of temporarily altered consciousness and abnormal behaviour in July 1993 and then he had repeated transient bouts of deep coma during the next 6 months despite intensive medications. He went abroad to receive a conventional liver transplant from a cadaveric donor in March 1994. While he was waiting for surgery severe encephalopathy recurred, and he died in April. The duration of illness was 21 months.

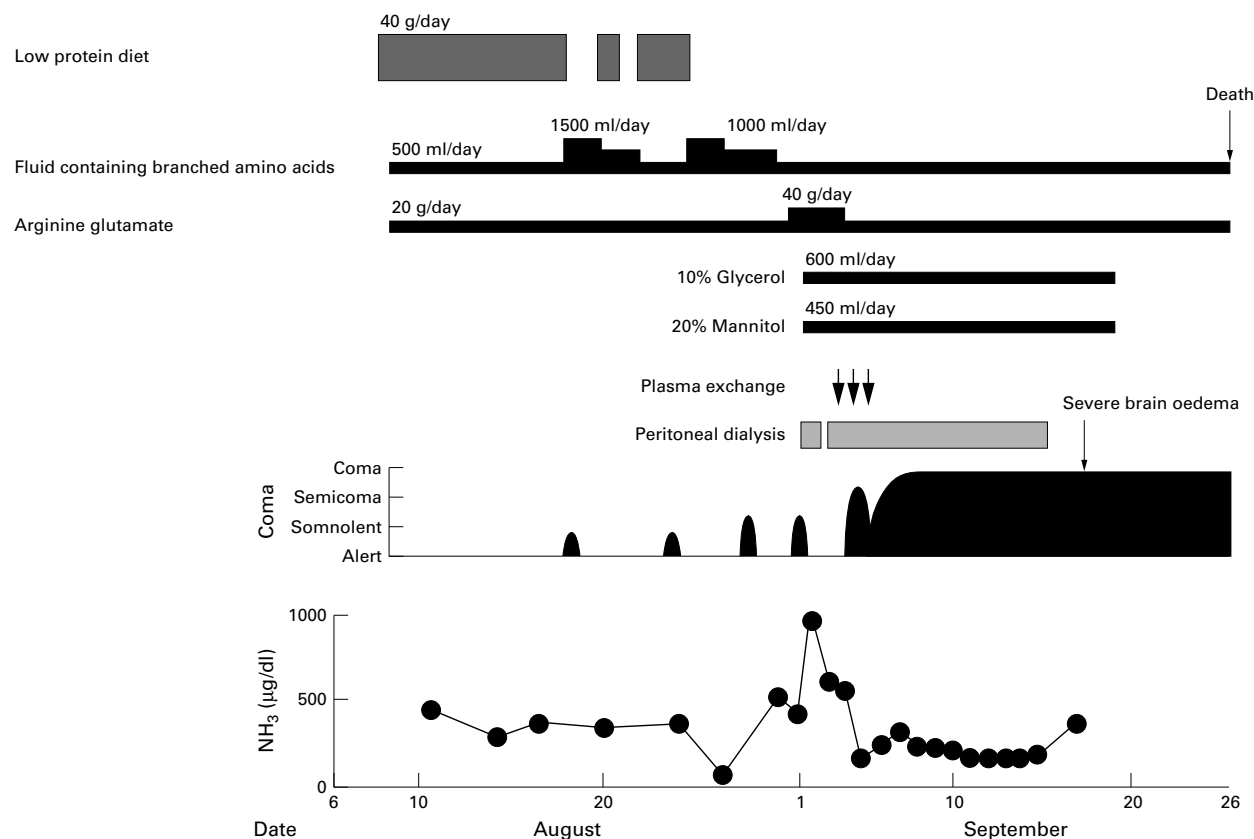


Figure 1 Clinical course of patient 1.

Patient 6

The patient was a 25 year old man with a 6 month history of this disease, showing recurrent attacks of unconsciousness. His parents were second cousins. He had a somewhat increased serum concentration of triglyceride (303 mg/dl). In June 1995 he had a liver transplant using a graft obtained from his 61 year old father. He started to work as a businessman again 10 months after the operation. During the postoperative 5 years he has not experienced any serious psychophysical problems. This was the first patient with citrullinaemia to be successfully treated by liver transplantation from a live donor.¹⁰

Patient 7

At the age of 43 this patient was admitted to another hospital because of severe epigastric pain. A raised serum concentration of amylase was found (652 IU/l, normal <120 IU/l) and he was diagnosed as having relapsing chronic pancreatitis. At the same time he was found to have a highly increased concentration of serum triglyceride (751 mg/dl). In October 1995, when he was 44, he had his first attack of delirium. In September 1996 the patient, aged 45, underwent liver transplantation using a graft obtained from his 20 year old son. He

started to work again 6 months after the operation, and none of his neurological symptoms have recurred during the postoperative 4 years.

Patient 8

This female patient had had chronic pancreatitis since her teens and underwent pancreaticojejunostomy at the age of 17. In August 1997, aged 23, she suddenly became comatose. Gait disturbance, difficulty in reading, and abrupt episodes of nausea and vomiting then appeared. She had a highly increased concentration of serum triglyceride (918 mg/dl). In March 1998, the patient, aged 24, underwent liver transplantation using a graft obtained from her 54 year old father. Since discharge she has been working in an office.

Patient 9

This female patient had been very fond of soybean products since childhood. At the age of 4 she had generalised tonic-clonic convulsions and had been treated with several types of anti-epileptic drugs, but still experienced occasional seizures. In April 1998 (at the age of 17) she developed attacks of unconsciousness with the intermittent appearance of violent hand tremor. Then her seizures became more severe even though she was taking medication. Liver transplantation was performed in September 1998. The donor was her father, aged 48. After

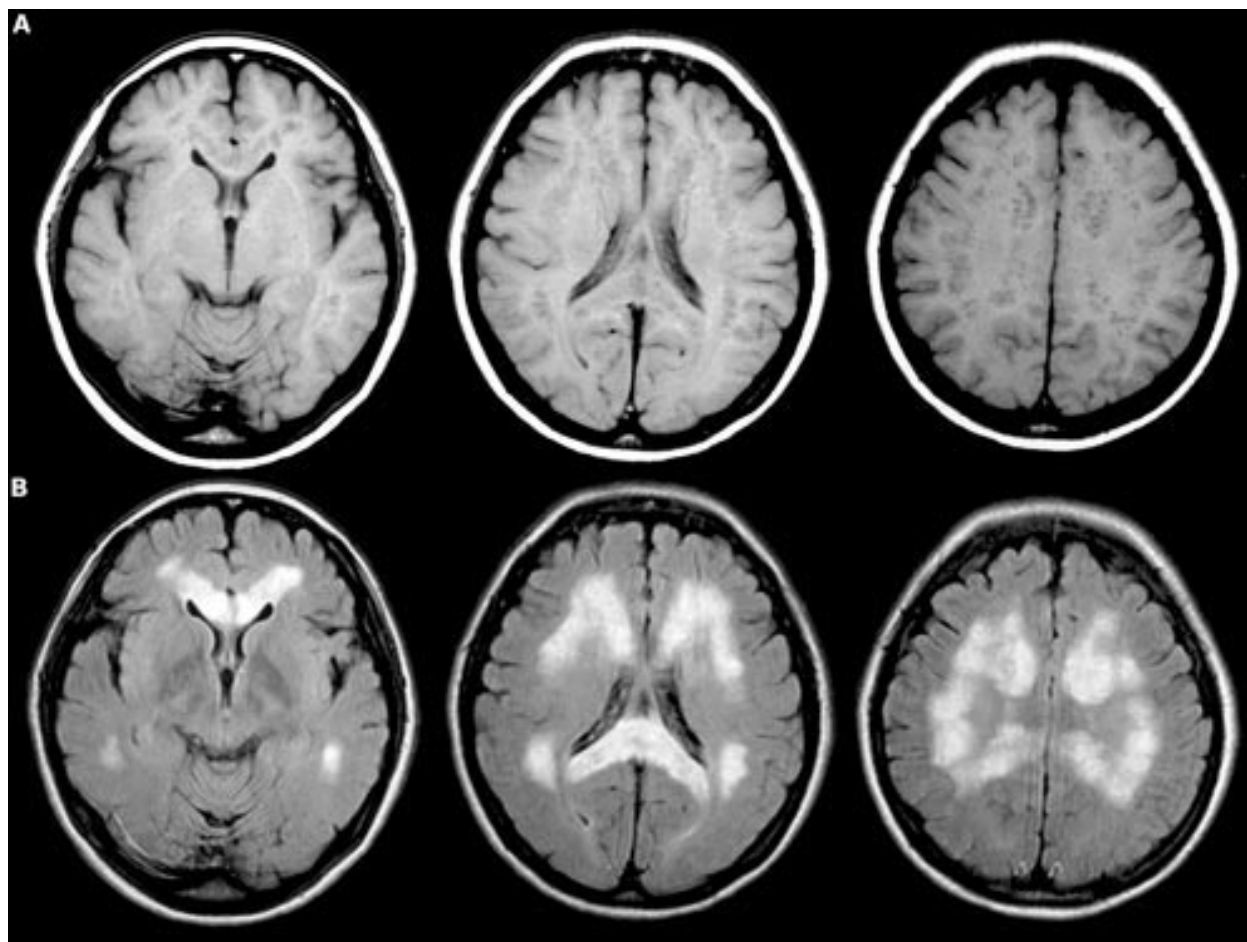


Figure 2 Brain MRI findings in patient 4. Spotty necrotic lesions with oedema are present in an extensive area of subcortical white matter and corpus callosum. (A) T1 weighted image; (B) T2 weighted image.

the operation, her mental activity improved and epilepsy has been well controlled by 1800 mg/day valproic acid.

Patient 10

This male patient was 32 years old. When he was 18 years old he was admitted to hospital because of acute pancreatitis. At the age of 19 he underwent a pancreaticojejunostomy but he still had occasional attacks of severe epigastralgia. At the age of 20 he was first affected by loss of consciousness and was started on therapy including a low protein diet (40 g/day). After the age of 30 episodes of unconsciousness recurred often, usually accompanied by the prodromal symptoms of blurred vision and

dysarthria. Finally he fell into a prolonged coma with violent flapping tremor in May 1999. In September 1999, he received a liver transplant using a graft from his 57 year old mother. He has been working after discharge.

EEG FINDINGS

Findings varied according to the state of consciousness of the patients: when they were alert EEG findings were normal, but when they were confused, the EEG showed diffuse slow waves including frequent discharges of triphasic waves. In addition to the appearance of these diffuse slow waves, occasional discharges of spike and wave complexes were seen in patients 3 and 9. After liver transplantation

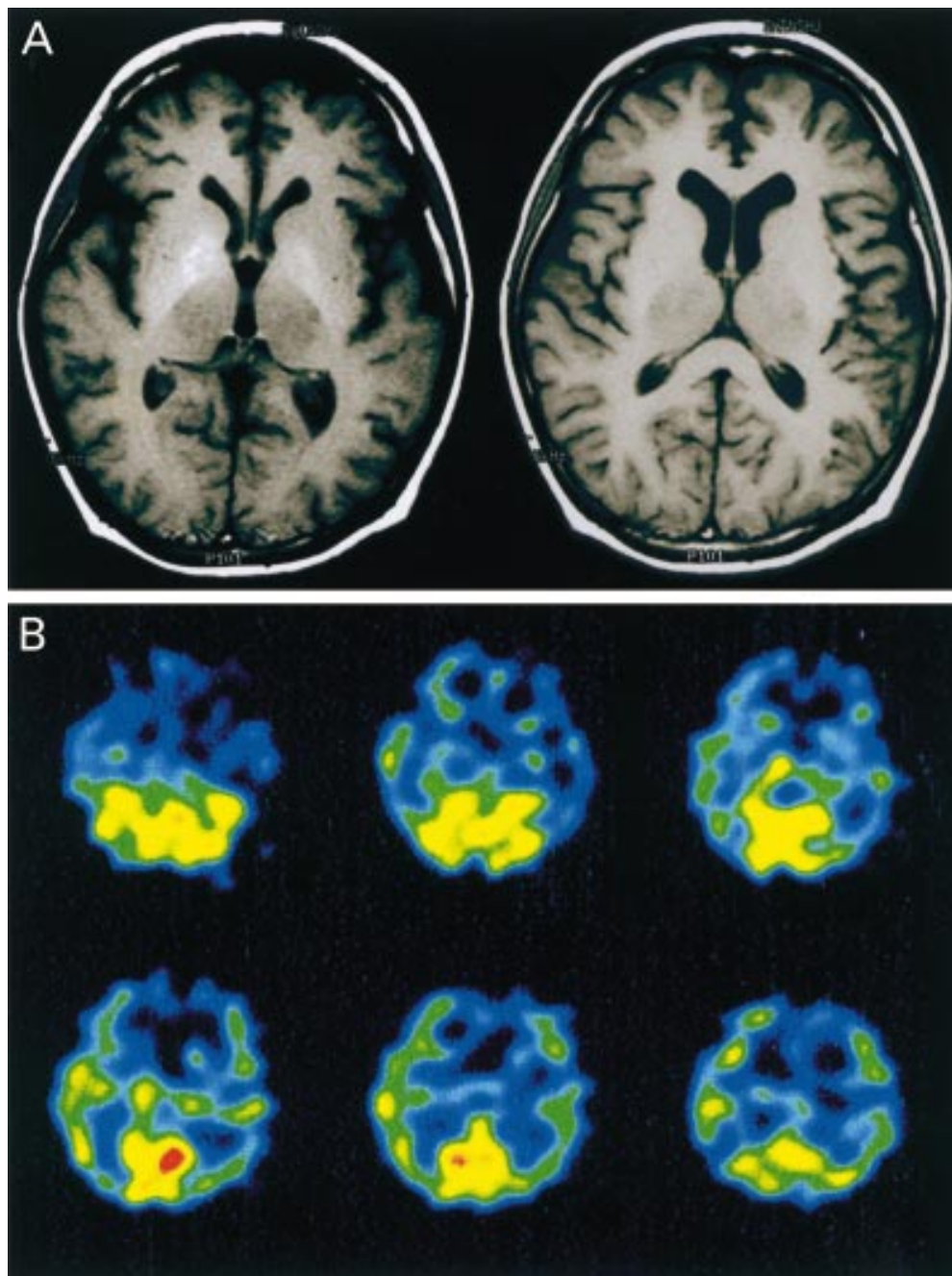


Figure 3 Brain MRI and SPECT findings in patient 3. (A) MRI on admission. Cortical atrophy in the frontotemporal lobe is apparent. (T1 weighted image). (B) Early images of ^{125}I -IMP SPECT in patient 3 taken 3 years postoperatively. Decreased uptake of isotope is still seen in an extensive area of the cerebrum, especially in the frontotemporal lobes.

these abnormal EEG findings disappeared within 3 months in five patients. In patient 9 the frequency of spike and wave complexes has been decreasing. In patient 4 triphasic waves were not seen but diffuse slow waves still remained 5 months postoperatively.

CT AND MRI IMAGES

On admission abnormal findings were seen in patients 3, 4, 9, and 10. The findings in patient 4 were mentioned above. In patients 3 and 10 slight atrophy of the frontotemporal cortices was noted (fig 3 A). In patient 9 diffuse cortical atrophy was seen, especially in the right parieto-occipital area. During follow up periods all findings in these four patients were unchanged.

¹²³I-IMP SPECT IMAGES

brain SPECT images were examined in patients 2, 3, 4, 5, 9, and 10. The scan was performed within 20 minutes of radiotracer injection. On admission patient 2 had a normal appearance, but the pattern had changed 3 years later, with a significant decrease in radionuclide uptake, especially in the cerebral cortices. Patient 5 showed a slight decrease in radionuclide uptake in an extensive area of the cerebral cortices and basal ganglia. In patients 3, 4, 9, and 10 the SPECT images were evaluated before and after liver transplantation: in the preoperative examination they disclosed a marked decrease in radionuclide uptake in an extensive area of brain, but in postoperative examinations no significant changes in radionuclide uptake were seen during 6 to 36 month follow up (fig 3 B).

LIVER FINDINGS

Abdominal CT was carried out on all patients at admission. Patients 2, 5, 7, and 8 showed a normal liver but the remaining six patients (patients 1, 3, 4, 6, 9, and 10) showed diffuse low density, indicating a fatty liver. No splenomegaly was seen. At gross examination at operation, the livers in all seven patients showed moderate to marked enlargement and looked yellowish and waxy. Histology commonly showed moderate to severe fatty metamorphosis.

Discussion

CLINICOPATHOLOGICAL FEATURES

Adult onset type II citrullinaemia (CTLN2) is now known to be one form of deficiency in urea cycle enzymes² and is caused by mutations of the citrin gene,¹⁶ but the original description of this disorder possibly dates back to the Japanese literature in the 1960s: Shiraki *et al*¹⁷ and Oda¹⁸ reported an unusual form of encephalopathy as a pseudoulegyria type of hepatocerebral disease. Their clinicopathological study involved eight men and three women whose ages ranged from 20 to 31. They commonly showed a sudden onset of consciousness disturbance, such as disorientation, restlessness, abnormal behaviour, and drowsiness, and at the same time a remarkable flapping tremor. Similar attacks repeatedly

appeared, and patients experienced convulsions, impaired cognitive functions, and limb paralysis in the more advanced stage. From 4 months to 2 years after onset, all patients were in "das appallische Syndrom" described by Kretschmer¹⁹ and also showed severe general emaciation. In four of them a raised concentration of plasma ammonia was detected and six patients had a history of a unbalanced diet, especially eating large amounts of peanuts or soybean products including tofu, a curd made from soybeans. At necropsy all brains showed marked gross atrophy, mainly in the temporo-parietal lobes. The characteristic histology was extensive and severe loss of cortical neurons without reactive gliosis, which was, therefore, called the pseudoulegyria type.^{17, 18} No abnormal vessels indicating the presence of portal-systemic shunt were found in the liver. Liver histology was described in six patients²⁰: two showed steatosis and the remaining four had severe fatty metamorphosis with slight to moderate fibrotic changes. In the late 1970s to early 1980s patients presenting with a clinical picture of the pseudoulegyria type of hepatocerebral disease were consistently shown to have very high concentrations of plasma citrulline in addition to hyperammonaemia,²¹ and a deficiency of ASS activity in the liver was found to be responsible for this disorder.^{22, 23}

Our 10 patients well satisfied the diagnostic criteria of type II citrullinaemia. The sex ratio was 6:4, being male dominant, and the age of onset of encephalopathy ranged from 17 to 51 years. On the basis of gene analysis the pattern of inheritance is autosomal recessive⁶ but consanguinity was present in only one of these 10 patients. Eight of our patients (1, 2, 4 to 8, 10) had rapidly progressive encephalopathy with fluctuations in consciousness disturbance, which was consistent with the typical clinical picture of type II citrullinaemia. On the other hand, the symptoms of patients 3 and 9 were different from the others. Patient 3 showed slowly progressive neuropsychic symptoms which clinically resembled the manifestations of major mood disorders or schizophrenia, and in an advanced stage she often had syncope-like attacks, involving loss of consciousness for 5 to 20 minutes. All of these psychic symptoms, including the syncope-like attacks, disappeared after liver transplantation, so they were attributed to the metabolic abnormalities in this disease. In patient 9 it is difficult to determine the onset of type II citrullinaemia because she had had intractable epilepsy since childhood, and convulsions sometimes appear as a symptom of encephalopathy in type II citrullinaemia. However, until the age of 17 she was not affected by severe encephalopathy, even though her history of epilepsy was longer than 10 years. Thus, the clinical manifestations of type II citrullinaemia probably started at this age.

Another notable finding is the presence of visceral organ lesions including chronic pancreatitis and severe fatty liver. The first was found in half of our patients and also preceded the development of encephalopathy in all five. One important cause of chronic pancreatitis in the patients with this disease is obstruction of

the main pancreatic duct, requiring pancreaticojejunostomy. Recently, it has been shown that the pancreatic secretory trypsin inhibitor (PSTI) gene is strongly expressed in the liver of patients with this disease,²⁴ and the serum level of PSTI was constantly high in the patients with type II citrullinaemia²⁵ including those we examined. Both findings suggest that the pathogenesis of this pancreatic disorder is linked to that of type II citrullinaemia. Severe fatty metamorphosis was also seen in all seven patients who underwent liver transplantation. Fatty liver develops in various pathological conditions: hyperlipidaemia, alcohol or drug intoxication, malnutrition, etc. Citrullinaemia itself might produce fatty metamorphosis, and the hypertriglyceridaemia seen in our four patients may have contributed to this fatty change. Moreover, nutritional factors, especially a low protein diet, also may play an important part.

THERAPEUTIC APPROACHES INCLUDING LIVER TRANSPLANTATION

From 1980 to 2000, 43 patients with type II citrullinaemia were reported in the Japanese literature.^{8,26} The male:female ratio was 34:9 and the age of onset ranged widely from 11 to 72 years, with a mean was 34.4 years.¹⁶ Most of these patients received conservative treatments, including a low protein diet, dietary arginine supplementation, administration of sodium citrate, sodium benzoate, lactulose, non-absorbed antimicrobial agents, and branched chain amino acid infusion. These treatments certainly produced temporary relief in the patients. However, the follow up data disclosed that 21 patients died within a few years of onset, and 14 of these 21 died between 3 days and 17 months later. The patients still alive might be affected by severe organic brain damage. Thus, the long term prognosis of patients with this disease treated with conservative therapy is obviously bad.

The optimal goal of treatment in metabolic encephalopathy is to correct the underlying abnormal metabolism in the patient before irreversible brain damage occurs. Urea cycle enzyme disorders are liver based metabolic disorders and liver transplantation is, therefore, an ideal treatment. Several patients with enzymatic disorders in the urea cycle underwent successful liver transplantation.²⁷⁻³⁰ For type II citrullinaemia, five patients were previously reported to have had liver transplants (three received from living donors in our country^{8,10,12} and two from cadaveric donors in foreign countries^{9,11}) and all five patients showed good postoperative courses. In this article we have described the therapeutic effects of living related liver transplantation in seven patients with type II citrullinaemia, with long term follow up in two patients. In these seven patients the metabolic abnormalities including hypercitrullinaemia and hyperammonaemia were immediately corrected after transplantation, and all neurological symptoms soon disappeared except in patient 10: this patient had had residual symptoms due to irreversible brain damage that occurred before operation,

but no additional symptoms have developed postoperatively. Six of them have been leading normal social lives without any specific medical support. Thus, liver transplantation has produced dramatic therapeutic effects in patients with this disease.

To investigate the postoperative changes in brain function in these patients serial examinations by EEG and SPECT were carried out in patients 3, 4, 9, and 10: the EEG was normalised in patients 3 and 10 shortly after transplantation, but the abnormal SPECT findings remained unchanged in all four, even though their clinical pictures were rapidly improving. They had possibly had irreversible brain injuries before transplantation, as supported by the fact that CT and MRI images of patients 3 and 10 showed slight but apparent cortical atrophy on admission. Finally, we emphasise that adult onset type II citrullinaemia is not rare in Japan and is a curable disorder.

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NEUROLOGICAL STAMP

Robert Debre (1882–1978)

Debre studied philosophy and, later, medicine. He subsequently became a professor of bacteriology and paediatrics.

In 1935 Debre (with Semelaigne) described a clinical syndrome resembling myotonia congenita but associated with cretinism. Debre syndrome is the enlargement of muscles caused by cretinism. Debre was honoured philatelically by France in 1981, which was the 100th year of his birth (Stanley Gibbons 2517, Scott B545).

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