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Carnitine status before and after paracentesis in patients with ascites and liver cirrhosis and improvement of subjective symptoms by intravenous administration of carnitine — Initial study

Naoki Hotta

Department of Internal medicine,Division of Hepatology,Masuko Memorial Hospital; 35-28 Takebashi Nakamura-ku,Nagoya,Aichi,Japan 453-8566

Introduction: Recently, carnitine has been reported to be useful for improving blood ammonia and cognitive function in cirrhotic patients with subclinical hepatic encephalopathy In Japan, levocarnitine has become available, and there have been several reports in which the carnitine concentration was first measured and whether symptomatic patients improved or not . And, the examination of symptomatic state around the ascites centesis was also carried out.

Method: Total carnitine concentration was measured in 5 cirrhotic patients undergoing ascites drainage during our hospital ambulatory, and after ascites drainage, intravenous administration of ercarnitine was conducted to examine whether or not the symptoms improved. Carnitine concentrations were measured before and after dialysis in four non-dialysis patients and one dialysis patient. Oral carnitine was administered in 3 patients (1 dialysis patient) because symptoms of cramps were noted, but in 2 cases. It was administered only after ascites drainage.

Case presentation: The case was in a 55 year-old male. The chief complaint was persistent ascites, cramps and general malaise. The patient had a medical history of treatment with radiofrequency ablation (Radiofrequency: RFA) for hepatocellular carcinoma. The patient had been followed up at another hospital for chronic liver cirrhosis type C. Interferon therapy was performed for liver cirrhosis, resulting in a virological complete response (sustained virological response: SVR). The ascites storage was

***Correspondence to Author:**
Naoki Hotta
Department of Internal medicine,Division of Hepatology,Masuko Memorial Hospital; 35-28 Takebashi Nakamura-ku,Nagoya,Aichi,Japan 453-8566

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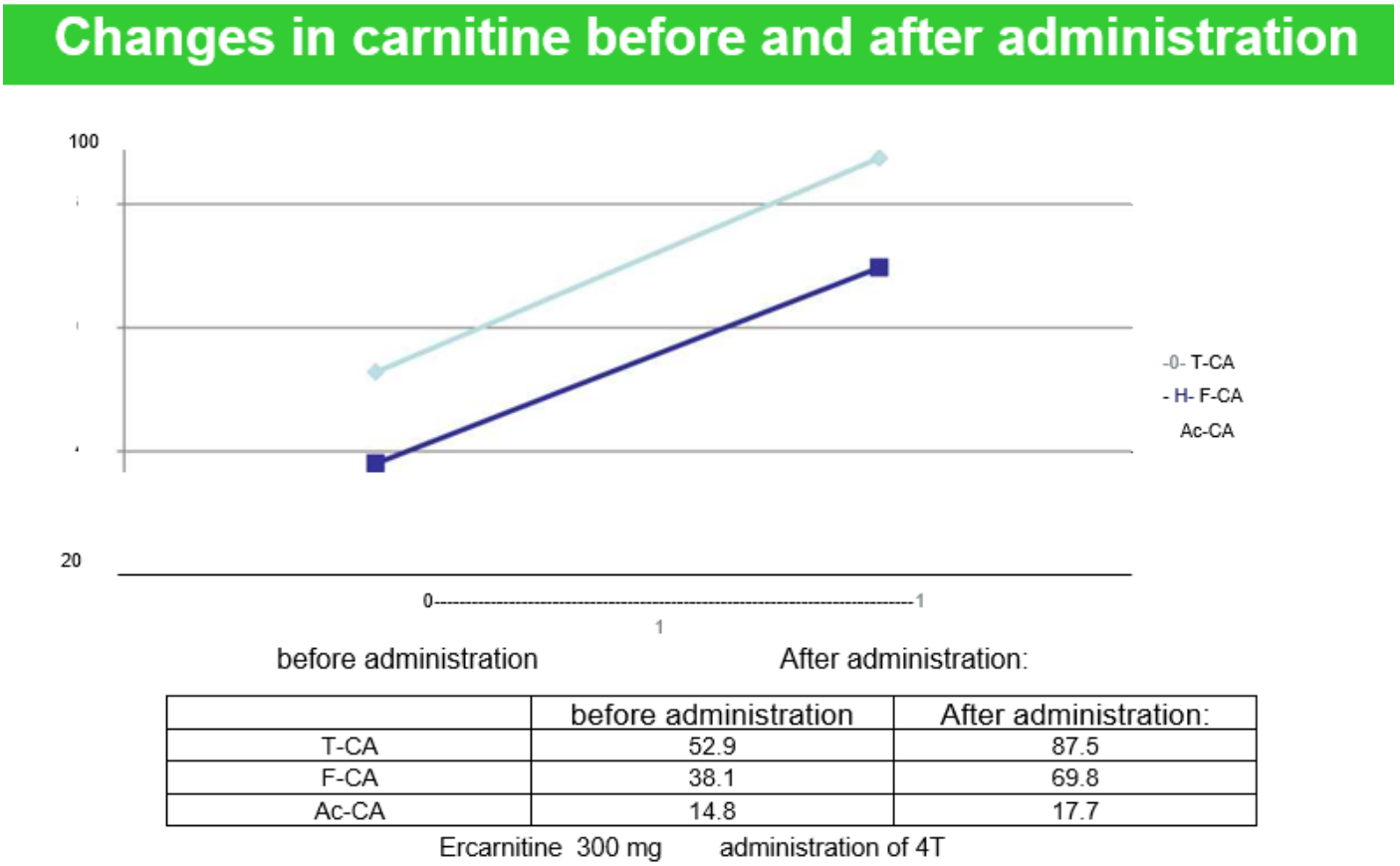
obvious, but the round was repeated from 2 to 3 times a week of golf. Because of frequent leg cramps during and at the end of golf, patients were given branched-chain amino acid preparations and liver protection drugs as oral medications. In a patient with liver cirrhosis, improvement of hepatic encephalopathy associated with decreased carnitine level and decreased ammonia were reported, and deterioration of muscle symptoms associated with carnitine deficiency in a dialysis patient was also reported [1-3]. Therefore, [4] Carnitine concentration and acylcarnitine/free carnitine ratio were measured in this patient, and administration of ercarnitine preparation was started. The carnitine concentration was within the normal range for total carnitine, acylcarnitine, and free carnitine, and the carnitine ratio was not below 0.4, which is the criterion for abnormal values.5).



	before administration	After administration:
T-CA	52.9	87.5
F-CA	38.1	69.8
Ac-CA	14.8	17.7

Fig 1 Carnitine concentration 1 month after administration of carnitine was increased in all cases, and the ratio of acylcarnitine/free carnitine was also decreased (0.388 to 0.253).

Administration of carnitine preparation was started from 600 mg of ercarnitine. Three days later, the patient's cramps improved. The appearance of the symptom could not be recognized during and after golf. Carnitine concentration 1 month after administration of carnitine was increased in all cases, and the ratio of acylcarnitine/free carnitine was also decreased (0.388 to 0.253). Carnitine concentration 11 months after administration

increased in all cases, and the ratio of acylcarnitine/free carnitine was slightly increased, but was 0.4 or less (Fig 1). The patient is currently hospitalized and discharged from the hospital after drainage of ascites. Ascites drainage was performed once or twice a week. Carnitine administration after ascites drainage increased the carnitine level without cramping or general malaise (Fig 2).

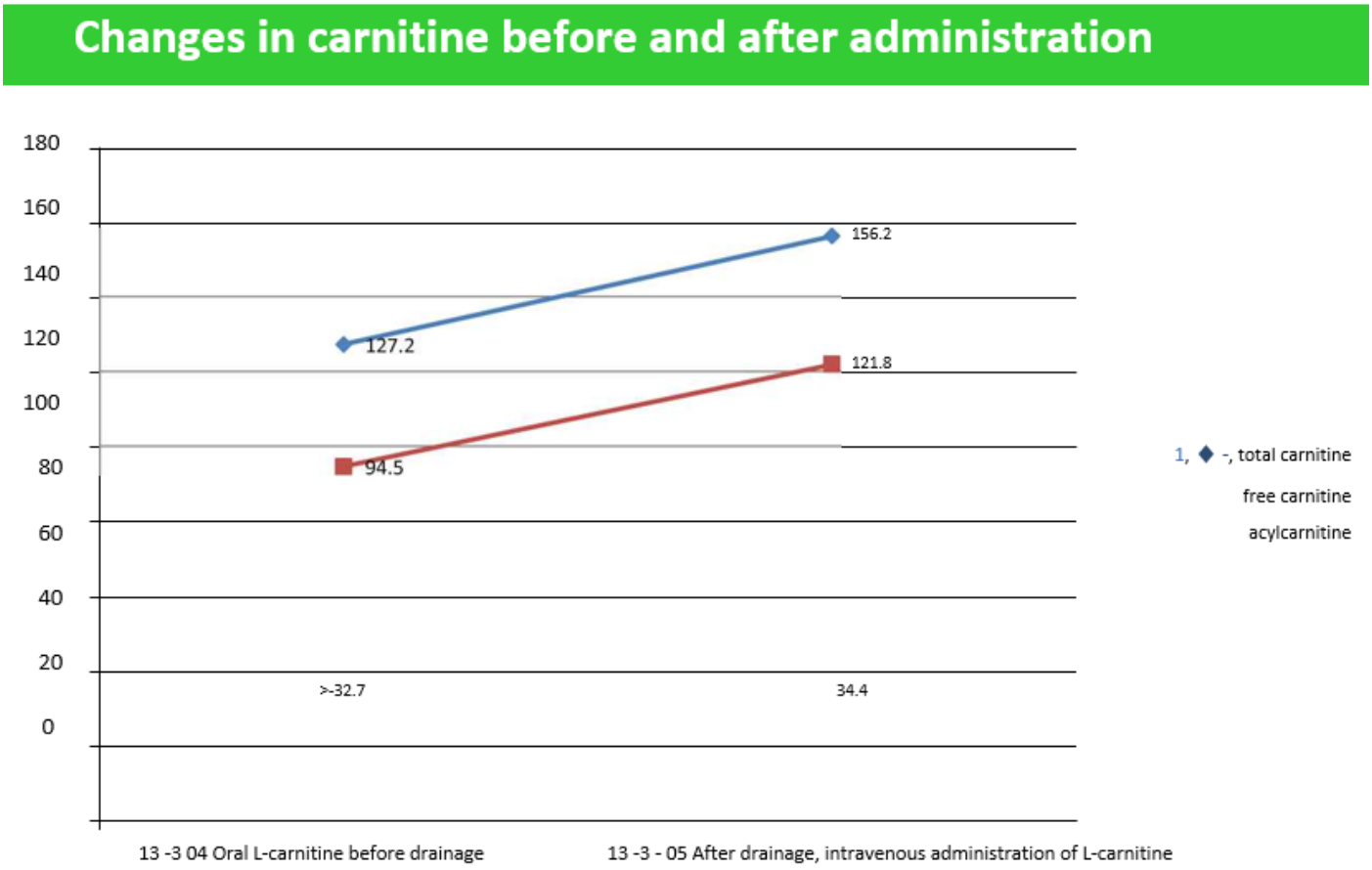


Fig 2 Carnitine administration after ascites drainage increased the carnitine level without cramping or general malaise

Result

The total carnitine concentration was within the normal range in the non-dialysis patients, and the concentration of carnitine decreased in the dialysis patients before and after dialysis. Though in 5 cases examined this time, after ascites drainage of 1 case (non-dialysis patient), there was a symptom of the muscle cramp, the appearance of the symptom could not be recognized on the day when this pharmaceutical was administered.

Consideration

Carnitine is a low-molecular-weight amino acid derivative that Takayanagi argues is important in energy metabolism [6]. For three reasons, one is essential for the transport of long-chain fatty

acids into mitochondria. The second regulates the ratio of CoA/acylCoA in mitochondria. Replacement of CoA with carnitine generates free CoA in mitochondria. Third, the acyl compound, which is a cytotoxin, is removed from the cells as a carnitine ester and excreted in urine.

Carnitine deficiency is classified as primary or second [7]. Primary carnitine transporter disorders (generalized carnitine deficiency) are congenital carnitine transporter disorders and secondary carnitine disorders are other inborn errors of metabolism or acquired medical conditions 1. Decreased synthesis (Cirrhosis, chronic kidney disease, etc.) 2. Decreased intake (Long-term parenteral nutrition (total potential transition: TPN) management, malnutrition, etc.) 3. Decreased body stores (Pregnant and breastfeeding women, very premature infants, etc.) Medical practices (dialysis, drug-induced). In this case, it is considered that liver cirrhosis is the basis of secondary deficiency, and the carnitine level was within the normal range. However, symptoms of carnitine deficiency are considered to have been present because the administration of ercarnitine improved the symptoms. The development of symptoms of cramps in patients with liver cirrhosis is occasionally observed as one of the adverse reactions. As therapeutic agents, improvement of symptoms may be observed by switching from branched-chain amino acid (branched chain amino acid: BCAA) preparations or BCAA granule preparations to oral nutrition for hepatic failure [8]. It has also been reported that the cause of muscle cramps is peripheral neuropathy, a myogenic mechanism, and a decreased blood concentration of taurine, which suppresses abnormal excitation at the neuromuscular junction. According to Goto et al., administration of BCAA improves the symptoms by decreasing the concentration of free L-tryptophan by increasing the concentration of serum albumin, and by promoting taurine synthesis by correcting the amino acid imbalance. [9]. In this case, oral administration of BCAA granule preparation was possible, but it was difficult to take oral nutrient for liver failure even after ascites drainage due to abdominal distension. Similarly, carnitine deficiency occasionally causes muscle symptoms in dialysis patients [4]. In the 10 study by Sakurauchi et al., 30 maintenance dialysis patients were orally administered 500 mg of L-carnitine over 12 weeks to investigate their physical symptoms. As a result, 2/3 of patients reported improvement in muscle symptoms (Malaise, muscle cramps, muscle aches, etc.). It is said that in dialysis patients with muscle cramps caused by carnitine deficiency, the concentration of carnitine in the blood and muscle decreases, causing a shift from fatty acids to sugars and proteins in the muscle cells (Decreased ATP production due to abnormal fatty acid metabolism and carnitine deficiency in muscle tissue). As a result, sufficient energy production is not achieved in the muscle cells compared to healthy people, and the burden on individual cells increases, resulting in muscle

symptoms. With L-carnitine administration, long-chain fatty acids are again fully utilized, and intracellular acyl compounds are washed out and normalized by carnitine, which is considered to be involved in the improvement of muscle symptoms [4,11]. Changes in muscle fibers have also been investigated in dialysis patients and in patients with carnitine deficiency, but there are no characteristic changes [12,13]. However, when carnitine is administered to these patients, an increase in the fiber length of type 1 muscle fibers is observed. These reactions indicate that type 1 muscle fibers are rich in mitochondria and that their metabolism is aerobic. Therefore, carnitine treatment is beneficial in type 1, increases the uptake of fatty acids into mitochondria, increases intracellular metabolism, increases muscle fiber length, and decreases the proportion of atrophied muscle fibers in all muscle fibers. [14]. Although muscle biopsy was not performed in this case, improvement of the symptoms was thought to be achieved by this mechanism.

Conclusion

The case in which the muscle cramp disappeared in the liver cirrhosis patient with the ercarnitine administration was experienced. The dose and duration of treatment should be considered in future studies. Also, since the serum carnitine fraction is not currently covered by insurance, it is necessary to search for substitute test items in the future.

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