Orthodox Sometimes Generates Paradox

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Digitalis has been used for many heart failure patients but digitalis itself may aggravate heart failure due to arrhythmia induced by its intoxication. Branched chain amino acid can dramatically improve hepatic coma in patients with hepatic failure but consciousness disturbance may be exacerbated by the branched chain amino acid itself due to development of uremia and acidosis in cases complicated with renal dysfunction. Thus a drug in itself may sometimes induce adverse events completely opposite to its main effect in itself and the cessation of the drug should be the first treatment for these patients.

Adult-onset type II citrullinemia (CTLN2) has been vigorously studied by Japanese scientists, Saheki T and Kobayashi K in Kagoshima University. They cloned the gene SLC25A13 encoding the protein “citrin” which is a transmembrane transporter protein, aspartate/glutamate carrier (AGC) and the causative gene of CTLN2 (1, 2). Aralar 1, which has 70% homologous protein to citrin is also an AGC; it was independently found by del Arco et al (3) but the difference in its expression distribution has been noticed. Citrin is expressed in many tissues (1) but most abundantly in liver, while aralar 1 is found mainly in the heart, skeletal muscle and brain (3–5). Severe brain edema is a main cause of death in patients with CTLN2. Mutation of citrin gene causes the cytoplasmic unbalance of NADH/NAD+ and may induce the edematous change of the brain. Yazaki et al (6) reported the adverse effect of glycerol on the treatment of encephalopathy in patients with CTLN2 in this issue.

See also p 188.

Most of the clinicians routinely use glycerol and mannitol for the treatment of brain edema without any specific attention except for fructose intolerance. They noticed a different outcome in the treatment of brain edema with glycerol and mannitol in patients with CTLN2; most of those treated by glycerol resulted in death (6). The mechanism of both drugs for the reduction of the intracranial pressure is based on osmotic pressure, namely these agents keep osmotic pressure in the blood vessel and the pressure gradient increases water influx from the tissue to blood stream. The authors speculated that the different outcome might be caused by their metabolic pathway (6). They postulate the adverse effect of glycerol metabolite, glycerol 3-phosphate which is metabolized to pyruvate and increases NADH/NAD+ ratio (Fig. 5 in ref 6). Furthermore, the fructose contained in the glycerol solution to prevent the hemolysis was thought to increase the NADH/NAD ratio may aggravate brain edema. On the other hand, most mannitol is not metabolized in the body, and it is excreted from the body in its original form without any reabsorption. These differences may actually cause the different outcome but some mannitol solution contains fructose as same as glycerol solution, mannitol without fructose would be safer. Before the mechanism of the worsening of brain edema induced by glycerol was precisely clarified, its use in CTLN2 was prohibited based on an epidemiological survey. The contraindication for glycerol for CTLN2 has already been appealed as safety information by the Japanese Ministry of Health, Labor and Welfare in August 2004 due to the effort by Yazaki et al but if the diagnosis was not correctly made, glycerol would be administered to the patient. Patients with CTLN2 might not be correctly diagnosed because the patients sometimes suddenly lose consciousness and are occasionally sent to the psychiatric department with convulsive seizure or disorientation. It is important to keep CTLN2 in mind when we see a patient with sudden onset consciousness disturbance in an adult accompanied by liver dysfunction with hyperammonemia.

CTLN2 was thought to be more prevalent in Japan but such patients have been found worldwide. The discovery of many mutation sites in citrin gene has clarified the surprisingly high mutation carrier rate not only in Japan (1/69) but in China (1/79), Taiwan (1/98) and Korea (1/50) (7). Knockout mouse of citrin has not yet shown the similar brain edema nor argininosuccinate synthetase (ASS) deficiency (8). Citrullinemia is still a mysterious disease (9) and further investigation will reveal the mechanism of the functional loss of ASS and the compensation system of AGC. I hope the elucidation of the molecular mechanism of CTLN2 will open the door of gene therapy, which is able to avoid liver transplantation (9, 10).

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References


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