Case Report

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Oral sodium phenylbutyrate for hyperammonemia associated with congenital portosystemic shunt: a case report

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Abstract

Objectives: The efficacy of sodium phenylbutyrate (SPB) for hyperammonemia associated with congenital portosystemic shunt (CPSS) remains unknown. We show the effectiveness of oral SPB.

Case presentation: Our patient had CPSS with severe hypoplasia of extrahepatic portal veins. At 9 months of age, to assess the efficacy of oral SPB, we evaluated the 24 h fluctuations of venous ammonia levels. In the first two days without SPB, ammonia levels were above 80 $\mu\text{mol/L}$ for half a day. On the third and fourth days, administration of oral SPB three times a day decreased ammonia to acceptable levels, except at midnight. On the fifth day, another oral SPB administration at 8 pm decreased ammonia at midnight. Low levels of branched-chain amino acids, as well as coagulation disturbances, were observed without apparent symptoms. At 12 months of age, he showed normal psychomotor development.

Conclusions: Oral SPB may be effective for hyperammonemia associated with CPSS.

Keywords: congenital portosystemic shunt; hyperammonemia; sodium phenylbutyrate.

Introduction

A congenital portosystemic shunt (CPSS) causes peripheral blood elevations in galactose, ammonia and bile acids because blood from the intestine bypasses the liver and flows into the inferior vena cava via the shunt vessel [1, 2]. Infants with CPSS need sufficient protein intake for appropriate growth. Blood ammonia levels must be kept at acceptable levels for normal neurological development until spontaneous closure of the shunt vessel, surgical shunt closure or liver transplantation. Despite a clinical demand, management for hyperammonemia before surgical treatment has not been established.

Sodium phenylbutyrate (SPB) reduces blood ammonia levels by forming phenylacetylglutamine, which is excreted into the urine [3, 4]. While oral SPB has been proven to reduce blood ammonia levels for urea cycle disorders [3, 4], its efficacy for hyperammonemia associated with CPSS remains unknown. Here, we report the effectiveness of oral SPB in reducing blood ammonia levels in an infant with CPSS.

Case presentation

The patient, a male baby, was the third child of healthy non-consanguineous Japanese parents. The pregnancy was unremarkable. He was delivered at term without asphyxia, with a birth weight of 2964 g (-0.1 SD) and a length of 50.5 cm ($+0.7$ SD). Neonatal mass screening, performed at four days after birth, revealed hypergalactosemia with normal enzyme activities responsible for galactose degradation, based on the results of filter paper blood examinations; galactose 21.5 mg/dL, galactose-1-phosphate 20.6 mg/dL, negative Beutler test, and negative galactose epimerase deficiency test. Total blood bile acid levels were elevated, while ammonia levels were within normal limits, 104 $\mu\text{mol/L}$ (reference for neonates, <110). At 14 days of life, regular formula and breast milk

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were discontinued and lactose-free formula was started. In a week, both galactose and galactose-1-phosphate levels decreased to 0.1 mg/dL. CPSS with extrahepatic shunt vessels was diagnosed by contrast computed tomography. Cardiac ultrasonography revealed a 5 mm atrial septal defect. At 2 months of age, an internal jugular vein catheterization revealed that the extrahepatic portal veins were severely hypoplastic. We waited for the extrahepatic portal vein to grow without further treatment. Later, blood total bile acids and ammonia levels gradually increased, while galactose levels remained low. At 4 months of age, his body weight and length were 6.55 kg (−1.0 SD), and 65.5 cm (−0.1 SD), respectively, although he consumed 75 kcal/kg/day (2.0 g/kg/day) of protein. He suffered from constipation, and picosulfate treatment was initiated to reduce intestine-derived ammonia. At 6 months of age, lactose-free baby food was started. Around 8 months of age, he showed poor weight gain, his weight and length were 7.16 kg (−1.7 SD) and 70.5 cm (−0.1 SD), respectively, with 80 kcal/kg/day (2.2 g/kg/day of protein). The prothrombin time-international normalized ratio was prolonged, while albumin and cholinesterase were almost normal (Table 1).

When the patient was 9 months of age, the ammonia level rose above 80 $\mu\text{mol/L}$, which is the recommended upper limit for urea cycle disorders [5], and he was hospitalized to control ammonia levels. Diurnal rhythms of

venous ammonia levels were observed with baby food three times a day and lactose-free formula two times a day, at 3 and 8 pm containing 88 kcal/kg/day and 0.48 g/kg of protein each (i.e. 2.4 g/kg/day of protein). For the first 2 days before the initiation of SPB, ammonia levels were above 80 $\mu\text{mol/L}$ for half a day and remained above 50 $\mu\text{mol/L}$, the normal upper limit, for both days (Figure 1A). On day 3 and 4, with 100 mg/kg of SPB orally after every baby food, ammonia levels decreased remarkably in the afternoon, the evening and the early morning (Figure 1B). On day 5, the addition of 100 mg/kg of SPB at 8 pm decreased the peak level of ammonia at midnight (Figure 1C). Before the initiation of oral SPB, levels of branched-chain amino acids (BCAAs) were near lower limits of normal, and prothrombin time was prolonged (Table 1). Two days after the initiation of oral SPB, the BCAA levels did not decrease further (data not shown). No galactosemia was observed in 24 h fluctuations of galactose levels on days 1 and 4, and on day 5, with continuous glucose monitoring devices, no hypoglycemia was observed (data not shown). Liver transaminases and creatinine levels were stable (Table 1). The parents noticed a change in body odor. The odor was not unfavorable.

At 10 months of age, with no pulmonary hypertension and no heart failure, surgery for the atrial septal defect was performed before portosystemic shunt occlusion. Ammonia levels remained at acceptable levels. He had further

Table 1: Laboratory examinations associated with liver function.

Laboratory examinations	References for adults	Age, months				
		4	7	8	9 ^a	11
Total bile acid, $\mu\text{mol/L}$	<10	121.0	158.2	111.1	116.8	51.0
Ammonia, $\mu\text{mol/L}$	<50	57	63	54	93	55
Albumin, g/dL	4.1–5.1	3.6	3.7	3.4	3.9	3.4
Cholinesterase, U/L	240–486	245	246	207	270	197
Prothrombin time-international normalized ratio	0.8–1.2		1.16	1.27	1.32	1.39
Aspartate transaminase, U/L	13–30	46	80	49	59	34
Alanine transaminase, U/L	10–42	29	33	24	24	12
Blood glucose, mg/dL	73–109		88	66	68	72
Creatinine, mg/dL	0.14–0.30	0.19	0.19	0.19	0.20	0.17
Plasma amino acids						
Glutamine, nmol/mL	365.7–855.5	673.6		560.5	621.8	417.6
Aromatic amino acids						
Tryptophan, nmol/mL	29.3–77.5	51.9		54.9	82.3	34.2
Phenylalanine, nmol/mL	30.2–91.9	136.1		85.3	74.0	70.5
Tyrosine, nmol/mL	34.0–98.8	265.9		158.7	136.8	128.7
Branched chain amino acids						
Valine, nmol/mL	93.7–352.3	240.6		158.1	106.4	84.8
Leucine, nmol/mL	44.2–191.0	141.4		63.6	52.3	33.2
Isoleucine, nmol/mL	19.5–106.7	85.9		47.3	33.9	18.6
Fischer ratio	1.32–5.28	1.16		1.10	0.91	0.69

^aResults at 9 months of age were obtained before the initiation of oral SPB.

Figure 1: 24 h fluctuation of venous ammonia levels without and with oral SPB.

(A) The first 2 days without SPB. Ammonia levels were above 80 $\mu\text{mol/L}$ for half a day.

(B) On day 3 and 4 with oral SPB after every baby food, ammonia levels decreased, except at midnight.

(C) On day 5 with oral SPB added at 8 pm, ammonia levels decreased at midnight.

decreases of BCAA levels and the Fischer ratio, and coagulation disturbances worsened (Table 1). Around 12 months of age, he showed normal psychomotor development.

Discussion

Here, we demonstrated the effectiveness of oral SPB for controlling blood ammonia levels in an infant by comparing 24 h fluctuations in venous ammonia levels without (2 days) and with (3 days) SPB administration. To our knowledge, this is the first report showing the effectiveness of oral SPB for hyperammonemia associated with CPSS.

Venous ammonia levels in our patient showed diurnal fluctuations throughout 24 h, and the peak appeared at midnight. The elevations at 9 am and 1 pm were consistent with breakfast and lunch, respectively. It was unclear why the elevation associated with supper was not apparent and accompanied by the peak at midnight. We speculate that the ammonia levels in our patient were determined by several factors, such as physiologic fluctuations, the time and the amount of protein intake, the intestinal ammonia production, and the amount of shunted blood and secondary liver dysfunction. The 24 h fluctuations in venous ammonia in our patient indicated that evaluation of levels by random sampling, or during the daytime, may result in missing the peak of blood ammonia levels and underestimating the duration times of high blood ammonia levels. Thus, 24 h fluctuations should be evaluated to estimate the risk associated with high blood ammonia levels.

Acceptable ammonia levels were attained by oral SPB therapy in our patient, probably because of decreased basal ammonia levels. Elevation ranges after breakfast or lunch were unchanged before and after oral SPB therapy, possibly because intestine-derived ammonia bypassed the

liver. It is noteworthy that our patient showed severe hypoplasia of the extrahepatic portal veins and gradually decreasing levels of coagulation factors prior to oral SPB therapy, suggesting that he had a large shunt flow and secondary liver dysfunction. In a previous study, intravenous ornithine and phenylacetate, the metabolite of phenylbutyrate, were effective for controlling hyperammonemia of cirrhotic decompensated patients who are presumed to have both portosystemic shunt vessels and liver dysfunction [6]. Therefore, we speculated that oral SPB may be effective for controlling ammonia levels of CPSS patients even with a large shunt flow and moderate liver dysfunction.

Our patient developed body odor change and low BCAA levels, both of which were listed as side effects of SPB in drug documentation for SPB, and have been previously reported [7]; he also showed coagulation disturbances. Body odor change was tolerable, and neither dermatitis nor bleeding tendency were seen. Thus, we considered that adverse events of oral SPB were not serious. Low BCAA levels and coagulation disturbances are known as complications of CPSS [8, 9]. From 8 months of age, BCAA levels decreased and coagulation status gradually worsened; therefore these abnormalities at 9 months of age, before the initiation of oral SPB, were considered complications of CPSS. After the initiation of oral SPB, BCAA levels lowered and coagulation status worsened further. While we speculated that the main cause of low BCAA levels and coagulation disturbances after the initiation of oral SPB was liver dysfunction secondary to CPSS, we could not exclude the possibility that oral SPB was an exacerbating factor. Severely low BCAA levels may cause psychomotor retardation, and bleeding tendency should be avoided for surgical procedures. Thus, during oral SPB therapy for CPSS, BCAA levels and coagulation status must be closely monitored. When isoleucine levels are extremely low, essential amino acids should be supplemented.

Conclusions

We report the case of an infant with CPSS and hyperammonemia who was successfully treated with oral SPB. This case suggests that, with a careful observation of BCAA levels and coagulation status, oral SPB may be effective for controlling blood ammonia levels associated with CPSS. In order to avoid protein restriction and achieve good growth, medications which decrease intestine-derived ammonia can be supplemented with oral SPB. It remains to be clarified whether oral SPB treatment improves the neurological outcome in infants with CPSS.

Learning points

- Oral SPB may be effective for hyperammonemia-associated with CPSS, and can be added as a supplement to medications which decrease intestine-derived ammonia.
- During oral SPB therapy for CPSS, BCAA levels and coagulation status must be closely monitored.
- Diurnal fluctuations of blood ammonia levels should be evaluated in patients with CPSS to estimate the risk associated with hyperammonemia.

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Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical statement: This study has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the Institutional Review Board at Keio University School of Medicine (Institutional Review Board number 20150104). We obtained written consent from the patient's parent.

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