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Clinical report

Lack of impairment of amino acids transport through the blood brain barrier in Type I cystinuria with mental retardation

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Abstract

Cystinuria is known as a representative inherited metabolic disorder accompanied with mental retardation. We determined whether the amino acid transport into brain was impaired in a 13-month-old boy with serious developmental delay accompanied with cystinuria. Serum levels of cystine and arginine were decreased. On the other hand cystine and dibasic amino acids levels (ornithine, lysine and arginine) in cerebrospinal fluids were all within the normal range. Neurodevelopmental delay improved from DQ 79 to 106 except regarding movement (locomotion and hand exercise). A low level of serum arginine might influence brain and neuronal development.

Introduction

Cystinuria is known as a representative inherited metabolic disorder with mental retardation[1-3]. One in 5-20% of such patients with cystinuria are mentally retarded, with an IQ below 70[4]. Pathological correlation between cystinuria and neurological conditions is still undetermined. The amino acid transport into the brain is regarded to be impaired, as in the kidney and gastrointestinal tract[1]. Blasberg et al emphasized the similarity between amino acid transportation into the brain and the kidney[5]. However, the reason for this is unknown. We investigated whether the amino acid transport in cerebrospinal fluid was impaired in a patient with serious developmental delay and cystinuria.

Case report

A 13-month-old boy was admitted because of pneumonia. On admission developmental delay was noticed. He was born after a normal pregnancy (41 weeks and 4 days). His birthweight was 4,178 g, height 52 cm, and head circumference 35 cm. He had thrombocythemia as a neonate (the details were not known). His uncle had had a renal stone. He held his head at 2 months, sat alone at 5 months, and gripped objects at 7 month of age. Neurodevelopmental delay was noticed at the age of 1 year. He could neither turn over, crawl, nor walk without support. Muscle tonus was decreased. DQ (Developmental Quotient) was 79 measured by the Enjoji infantile developmental assessments. On admission his physical examination results at the age of 13 months were unremarkable. Facial dysmorphism and anomaly were not present. His laboratory findings (Table 1) showed no specific findings except for white blood cell counts. The results of examinations for TORCH syndrome were negative. Urinalysis, head CT, abdominal echogram and fundus examination revealed no irregularities.

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Table 1 Laboratory findings at the age of 13 months

WBC	/μl	16,900↑	ASLO	IU/ml	<60
RBC	104/μl	506	IgG	mg/dl	1,250
Hb	g/dl	12.7	IgA	mg/dl	116
Ht	%	39.0	IgM	mg/dl	268
PLt	/μl	13.9	IgE	IU/ml	102
AST	U/l	31	C_3	mg/dl	116
ALT	U/l	11	C_4	mg/dl	40
TP	g/dl	7.7	CH_{50}	U/ml	54.7
T-Bil	mg/dl	0.51			
D-Bil	mg/dl	0.1	Rubella IgM (FA)		(－)
I-Bil	mg/dl	0.41	Rubella (HI)		(－)
BUN	mg/dl	5.1	HSV-IgM(FA)		(－)
Creatinin	mg/dl	0.2	CMV-IgM (FA)		(－)
Glucose	mg/dl	109	Toxoplasma IgG		(－)
Na	mEq/l	143	Toxoplasma IgM		(－)
Cl	mEq/l	106	Toxoplasma IgM		(－)
K	mEq/l	3.8			
CRP	mg/dl	<0.3			
CPK	u/l	46			

Table 2 Analysis of amino acids

samples	age	unit	cystine	ornithine	lysine	arginine	tryptophan
urine	13 months	μmol/day	370.2 ↑ (20-200)	338.2 ↑ (7-50)	3493.8 ↑ (7-50)	172.2 ↑ (10-60)	47.8 (20-150)
urine (one point in a day)	18 months	μmol/day	2064.1 ↑ (20-200)	1046.3 ↑ (7-50)	14186.6 ↑ (7-50)	655.0 ↑ (10-60)	204.7 ↑ (20-150)
plasma	24 months	nmol/mL	20.8 ↓ (29-49)	70.9 (30-100)	170.9 (110-240)	47.4 ↓ (54-130)	64.3 (37-75)
cerebrospinal fluid	24 months	nmol/mL	ND (ND)	4.5 (2.84-19.17)	20.6 (11.61-36.47)	15 (11.92-31.0)	ND (ND)

( ) mean normal range. The control cerebrospinal fluids were obtained from patients without any CNS diseases. Other amino acids were all within normal ranges

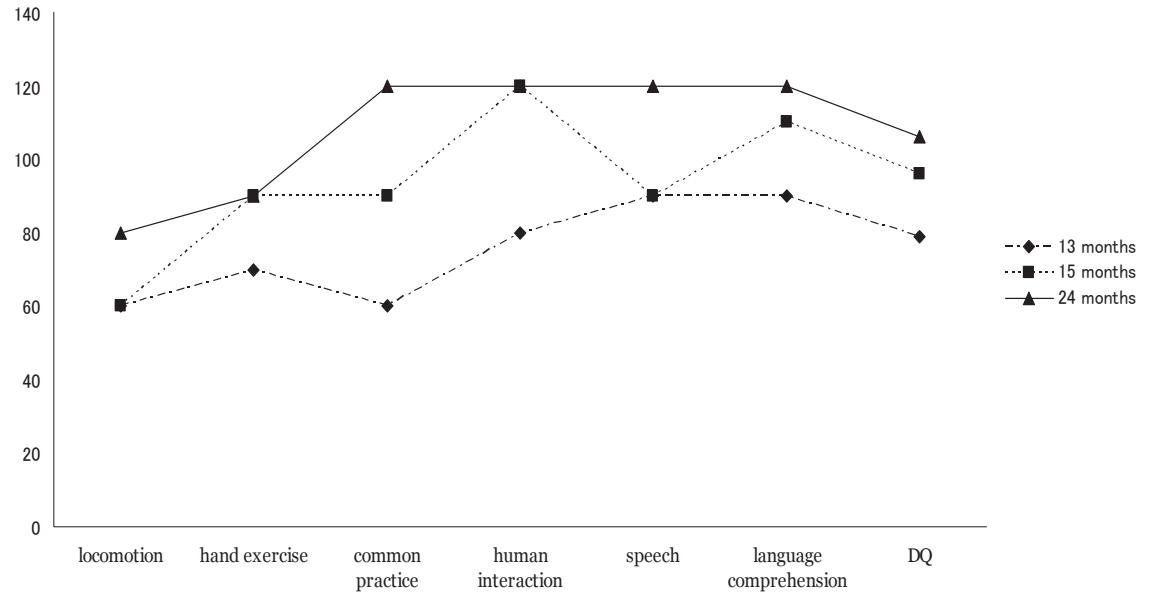

Fig. 1 The developmental quotient (DQ) were assessed by the Enjoji method (%)

Analysis of amino acids showed extremely high levels of cystine and dibasic amino acids (ornithine, lysine and arginine) in excreted urine. Serum levels of cystine and arginine were decreased to 20.8 (29–49) and 47.4 (54–130), respectively. On the other hand cystine and dibasic amino acids (ornithine, lysine and arginine) in cerebrospinal fluids were all within normal limits, which are shown in Table 2. Neurodevelopmental delay improved from DQ 79 to 106 except for movements (locomotion and hand exercise), as listed in Figure 1.

Discussion

Cystinuria is classified into three types as type 1 and non-type 1, which is also classified into type II and III according to the abnormality of absorption in the intestinal epithelium[6,7]. Since serum levels of cystine and arginine in this report were decreased, his disease was classified as type I. Type I cystinuria is known to be caused by a mutation in *SLC3A1*, located on chromosome 2p-16.3-21 eoncoding rBAT (related to $B^{0,+}$ amino acid transporter)[8]. Unfortunately we could not investigate his genome including amino acids. However, his family history suggested homozygous or double hetero mutation of *rBAT*[6,9].

Cystinuria is known as a representative inherited metabolic disorder with mental retardation and multi-system disorder including nephrolithiasis [10-12]. Impairment of amino acid transport into the brain is seems to cause mental retardation. However, the levels of amino acid including cystine and dibasic amino acids in cerebrospinal fluid were within the normal range in this case. Therefore impairment of amino acid transport into the brain did not directly cause his developmental delay.

The location of *rBAT* is distributed in the brain, kidney and intestine[13] and the impairment of cell membranes in neurons and glial cells might occur. Alternatively his plasma arginine level was lower than in normal cases. Arginine is a conditionally nonessential amino acid, meaning most of the time it can be manufactured by the human body, and does not need to be obtained directly through diet in adults. However, in infants the process of the synthesis of arginine is not mature. Therefore a lack of arginine might influence the development of brain and neuron, because arginine works as a precursor of nitric oxide (NO). NO from nNOS is a representative neurotransmitter. Alternatively low arginine might induce hyperammonemia, as was been reported in experimental models[14].

This is apparently the first report on amino acid in cerebrospinal fluid in a patient with cystinuria.

References

1) Scriver CR, Whelan DT, Clow CL, Dallaire L. Cystinuria : increased prevalence in patients with mental disease. N Engl J Med 1970 ; **283** : 783-786
2) Cavanagh NP, Bicknell J, Howard F. Cystinuria with mental retardation and paroxysmal dyskinesia in 2 brothers. Arch Dis Child 1974 : **49** : 662-664
3) Smith A, Procopis PG. Cystinure and its relationship to mental retardation. Med J Australia 1975 ; **2** : 932-933
4) Gold RJ, Dobrinski MJ, Gold DP. Cystinuria and mental deficiency. Clin Genet 1977 ; **12** : 329-332
5) Blasberg R, Lajitha A. Substrate specificity of steady-state amino acid transport in mouse brain slices. Archives of Biochemistry and Biophysics 1965 ; **112** : 361-377
6) Rosenberg L E, Downing S, Durant JL, Segal S. Cystinuria : biochemical evidence for three genetically distinct diseases. J Clin Invest 1966 ; **45** : 365-371
7) Lee EH, Kim YH, Hwang JS, Kim SH. Non-type I cystinuria associated with mental retardation and ataxia in a Korean boy with a new missence mutation (G173R) in the SLC7A9 gene. J Korean Med Sci. 2010 ; **25** : 172-175
8) Calonge MJ, Gasparini P, Chillarón J, Chillón M, Gallucci M, Rousaud F, Zelante L, Testar X, Dallapiccola B, Di Silverio F, et al. Cystinuria caused by mutations in rBAT, a gene involved in the transport of cystine. Nat Genet 1994 ; **6** : 420-425
9) Hashimoto K, Ando Y, Nakano C. I-III type double heterozygous cystinuria with delayed psychomotor development. No to Hattatsu **20** : 429-432, 1988
10) Dennis J, Taylor DC. Neurological complications of cystinuria. Dev Med Child Neurol ; **198022** : 402-403
11) Cochat P, Pichault V, Bacchetta J, Dubourg L, Sabot JF, Saban C, Daudon M, Liutkus A. Nephrolithiasis related to inborn metabolic diseases. Pediatr Nephrol 2010 ; **25** : 415-424
12) Martens K, Jaeken J, Matthijs G, Creemers JW. Multi-system disorder syndromes associated with cystinuria type I. Curr Mol Med 2008 ; **8** : 544-550
13) Jackman NA, Uliasz TF, Hewett JA, Hewett SJ. Glia. Regulation of system x(c)(-)activity and expression in astrocytes by interleukin-1β : implications for hypoxic neuronal injury. 2010 ; **58** : 1806-1815
14) Deshmukh DR, Thomas PE. Arginine deficiency, hyperammonemia and Reye's syndrome in ferrets. Lab Anim Sci 1985 ; **35** : 242-245

発達遅延を伴うシスチン尿症における正常脳内アミノ酸トランスポート

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シスチン尿症は発達遅延を伴う遺伝的な代謝異常の代表として知られている。今回、シスチン尿症に発育遅延を伴う 13 か月児において、アミノ酸輸送が正常であるかを検討した。血中のシスチンとアルギニンの値は減少していた。シスチンとアルギニンの血中濃度は減少していたが、髄液中の 2 塩基アミノ酸（オルニチン、リジンおよびアルギニン）はコントロールと比較し、正常域であった。患児の発達は運動（移動および手運動）を除いて成長とともに 79 から 106 と改善が認めたことから、乳幼児期の血中のアルギニンが低いことが脳や神経の発達の影響していた可能性が推察された。

〈キーワード〉 シスチン尿症、発達遅延、小児、血液脳関門、二塩基性アミノ酸