Case report 1

f.Abbasi

tums

- Male 8 y,
- First presentation:
- In 6 years old ,he diagnosed with lupus nephritis due to proteinuria and immunologic lab data and pathologic result after renal biopsy.
- In last hospitalization: he presented with central lupus with agitation, seizure and loss of consciousness ,he received methylprednisolone pulse in ICU.
- He suffered from growth retardation and chronic anemia and leucopenia

- In recent hospitalization in children medical center hospital, he presented with: seizure ,megaloblastic anemia, leukopenia,agitation and low-level consciousness ,
- Metabolic investigation:
- Serum aa hplc: high glutamine, low arginine, low ornithine ,low lysine.
- Urine chromatography :high lysine, arginine and moderate ornithine.
- Plasma ammonia: 280 mm/lit,146mm/lit,lactate :20
- Urine organic acid : orotic aciduria moderate
- Ms/MS: no pathologic change except for mentioned amino acids

- First Genetic testing: imerslund-grasbeck syndrome1
- After lab information and clinical sign and symptoms.
- Rechecked WES, and pathologic mutation in slc7a7 gene have been conformed.
- Treatment :with sodium benzoate , citrulline ,lysine, arginine and low protein diet
- And after stabilization of patient GH started for patient.
- Follow up level of lysine increased and cytotoxic drugs tapered ,
- Growth is developed and patient is under controlled.

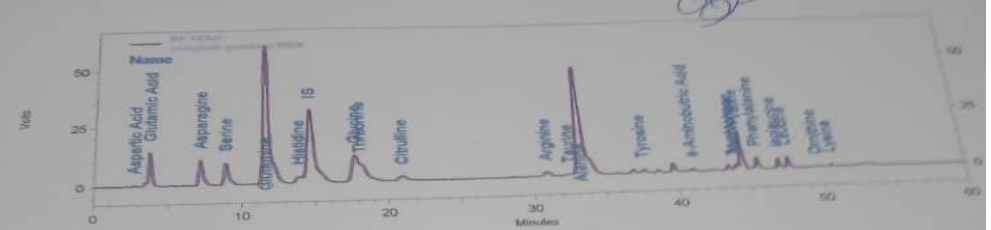
Case 2

- A female pateint ,age:13,
- First presentation:age 5 with proteinuria and immunologic disturbances and diagnosed with lupus nephritis,
- Multiple admission due to fever and low consciousness ,agitation , seizer ,and delusion in other centers.
- Medication: cellcept, hydroxychloroquine , prednisolone and captopril
- At last admission in this hospital(1402).presented with:
- Low consciousness, and delusion

- Metabolic consult urgent
- High plasma amonemia ,
- HPLC: lysine :17.5 (80-250)mic M /Lit
- Ornithine: 16.2 (20-135)mMol/lit
- Arginine: 8.9 (19-216) MmOL/lit
- Glutamine: 809.4 9396-746) mMol/lit
- Urine chromatography:
-
-

Method: HPLC/ Amino Acids Analysis
Patient: setayesh goodarzi 5804
Acquired: 1/30/2024 1:19:27 PM
Printed: 1/31/2024 11:46:00 AM

5804 -ستایش گودرزی



RF-10Axl Results

Name	Concentration (umol/L)	Normal Range (umol/L)
Aspartic Acid	4.1	0-20
Glutamic Acid	114.2	10-120 (up to 200 for 1-3 month)
Asparagine	101.4	24-60
Serine	107.9	60-200
Glutamine	809.4	396-746 (100-1200 for 1-3 month)
Histidine	102.2	50-130
IS	1.0	
Glycine	207.0	140-490 (80-320 for 1-3 month)
Threonine	95.5	40-240
Citrulline	35.2	8-47
Arginine	56.7	40-160 (10 -130 for 1-3 month)
Taurine	8.9	19-216
Alanine	924.3	240-600 (100-400 for 1-3 month)
Tyrosine	16.3	30-120
a-Aminobutric Acid	11.6	6-38
Tryptophane	12.0	15-73
Methionine	8.0	6-49 (5-30 for 1-3 month)
Valine	107.6	140-350 (70-280 for 1-3 month)
Phenylalanine	44.3	48-109 (20-80 for 1-3 month)
Isoleucine	44.7	30-130
Leucine	37.5	60-230 (35-180 for 1-3 month)
Ornithine	16.2	20-135 (10-110 for 1-3 month)
Lysine	17.5	80-250 (45-200 for 1-3 month)

Comment: IS=Internal Standard

Dear Colleague, The amino acid levels are influented by the childs age a
overnight fast(or at least 4-hours fast

Gene

آزمایشگاه دکتر شهروئی
ژنتیک و ایمونولوژی

GENETIC TEST REPORT

Patient ID:	PID2624-P	**Physician:**	Dr. Tahghighi/ Dr. Abbasi
Patient Name:	Setayesh Goodarzi	**Specimen Type:**	Peripheral blood
Date of Birth:	1388/5/15	**Reception Date:**	1402/11/10
Gender:	Female	**Report Date:**	1402/12/27

Test Performed

Whole Exome Sequencing, Performed by Macrogen Inc., South Korea, NovaSeqX plus 150PE 8Gb 69SPL, SureSelect V7-Post, 100X, Variant calling based on best practice of GATK. Genome ref version V. GRCh37.

Clinical Indications

The patient is product of a consanguineous marriage with renal disease and seizure

Results: Positive

A Variant of Uncertain Significance was identified

Variant Relevant to Indication for Testing

Gene	Variant coordinates*	Associated disease	Inheritance[a]	Zygosity[b]	ACMG/ClinVar Classification[c]
SLC7A7	**Chr14 23243292 23243292 A G:** NM_001126105.2:(10/11): c.1279T>C:p.Cys427Arg	Lysinuric protein intolerance 222700	AR	hom	VUS/NR

* :(/): Exon_Intron_Num/Exon_Intron_Tot. In case of exonic variation the numbers are referring to the exon and in case of intronic, referring to intron.
[a] **AD**=Autosomal Dominant; **AR**=Autosomal Recessive; **XL**=X-Linked; **XLR**=X-Linked Recessive; **DR**= Digenic Recessive
[b] **Hom**=Homozygous; **Het**=Heterozygous; **Hem**=Hemizygous; **WT**=Wild Type
[c] **VUS**=Variant of Uncertain Significance, **R**= Reported, **NR**= Not Reported

Interpretations

The protein encoded the *SLC7A7* gene is the light subunit of a cationic amino acid transporter. This sodium-independent transporter is formed when the light subunit encoded by the *SLC7A7* gene dimerizes with the heavy subunit transporter protein SLC3A2. This transporter is found in epithelial cell membranes where it transfers cationic and large neutral amino acids from the cell to the extracellular space.

The identified variant has not been reported in the ClinVar and based on the ACMG classification is Variant of Uncertain Significance.

Treatment

- Under observed

Case 3

Female 23 mo

- First presentation: at 9 Mo with respiratory infection and drowsiness
- Second hospitalization: with drowsiness and low consciousness

    Dx : encephalitis ,with supportive care ,discharge

Third hospitalization :after 4 Mo from second admission

With low consciousness ,restlessness

Metabolic consultation

Metabolic workup

- Amonia :1050 mcmol/l
- Dialysis performed

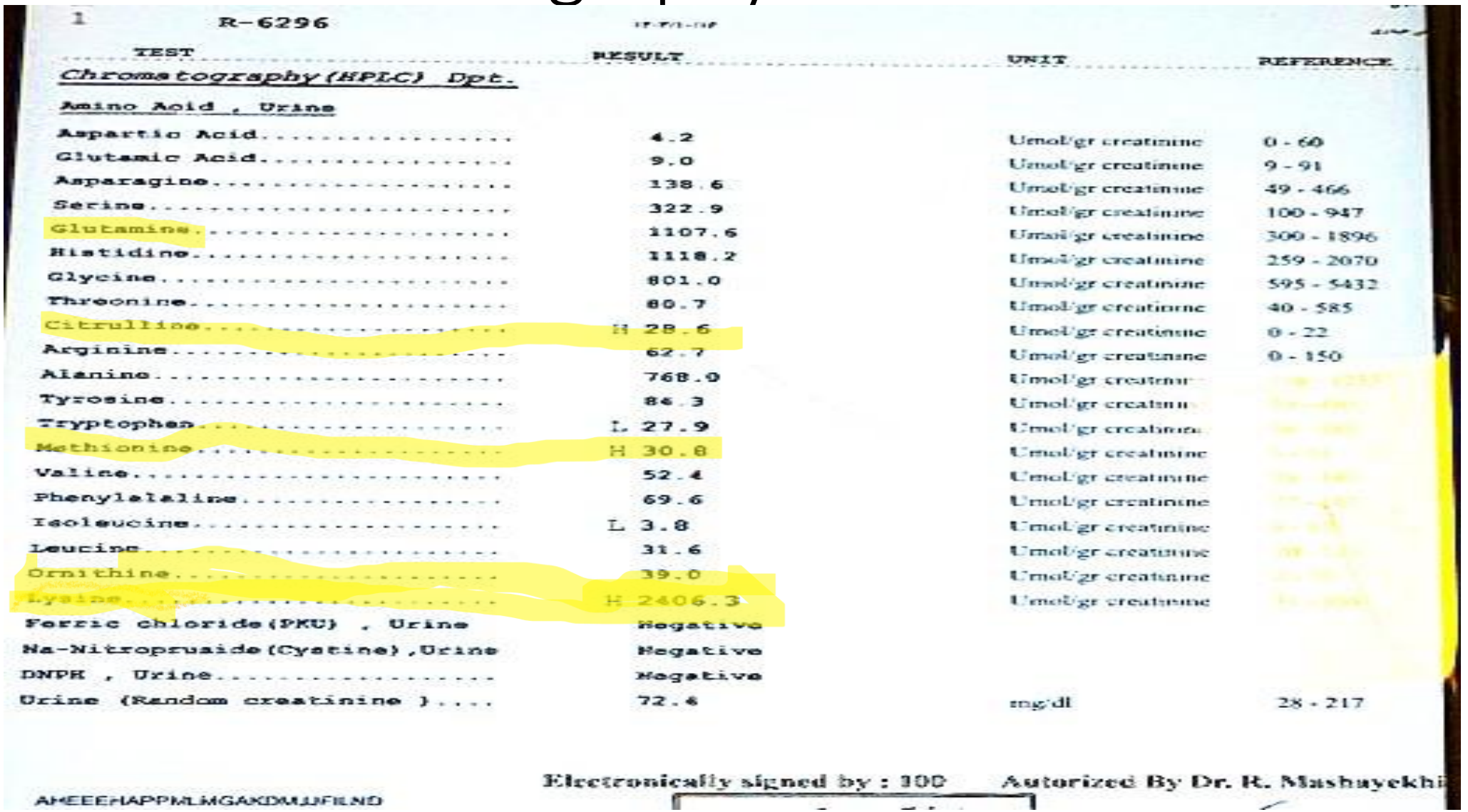
کد برگه : ۲۹۶۰۶۵۷ نام پدر: محمد تاریخ چاپ : ۱۴۰۳/۱۱/۰۱ ۱۴:۰۹

کد پذیرش : ۶۸۲۱۹۲۲ پزشک معالج: دکتر ———— بخش بستری Infant ICU - سن : ۲ سال نوع بیمه تامین اجتماعی-وصل به وت

HPLC(plasma)

Test	Result	Unit	Reference Value
Aspartic Acid	7.5	uMol/L	0-20
Glutamic Acid	83.6	uMol/L	10-120
Asparagine	35.2	uMol/L	24-60
Serine	108.4	uMol/L	60-200
Glutamine	753.6	uMol/L	396-746
Histidine	94.0	uMol/L	50-130
Glycine	130.9	uMol/L	140-490
Threonine	50.1	uMol/L	40-240
Citrulline	17.5	uMol/L	8-47
Arginine	29.8	uMol/L	40-160
Taurine	35.4	uMol/L	19-216
Alanine	268.8	uMol/L	240-600
Tyrosine	41.2	uMol/L	30-120
a-Aminobutric Acid	8.0	uMol/L	6-38
Tryptophane	22.0	uMol/L	15-73
Methionine	11.0	uMol/L	6-49
Valin	81.7	uMol/L	140-350
Phenylalanine	58.5	uMol/L	48-109
Isolucine	32.4	uMol/L	30-130
leucine	44.6	uMol/L	60-230
Ornitine	24.0	uMol/L	20-135
Lysine	48.4	uMol/L	80-250

Urine chromatography



1 R-6296

TEST	RESULT		UNIT	REFERENCE
Chromatography (HPLC) Dpt.				
Amino Acid , Urine				
Aspartic Acid	4.2		Umol/gr creatinine	0 - 60
Glutamic Acid	9.0		Umol/gr creatinine	9 - 91
Asparagine	138.6		Umol/gr creatinine	49 - 466
Serine	322.9		Umol/gr creatinine	100 - 947
Glutamine	1107.6		Umol/gr creatinine	300 - 1896
Histidine	1118.2		Umol/gr creatinine	259 - 2070
Glycine	801.0		Umol/gr creatinine	595 - 5432
Threonine	80.7		Umol/gr creatinine	40 - 585
Citrulline	H 28.6		Umol/gr creatinine	0 - 22
Arginine	62.7		Umol/gr creatinine	0 - 150
Alanine	768.9		Umol/gr creatinine	
Tyrosine	84.3		Umol/gr creatinine	
Tryptophan	L 27.9		Umol/gr creatinine	
Methionine	H 30.8		Umol/gr creatinine	
Valine	52.4		Umol/gr creatinine	
Phenylalaline	69.6		Umol/gr creatinine	
Isoleucine	L 3.8		Umol/gr creatinine	
Leucine	31.6		Umol/gr creatinine	
Ornithine	39.0		Umol/gr creatinine	
Lysine	H 2406.3		Umol/gr creatinine	
Ferric chloride(PKU) , Urine	Negative			
Na-Nitropruaide(Cystine) ,Urine	Negative			
DNPH , Urine	Negative			
Urine (Random creatinine)	72.4		mg/dl	28 - 217

Electronically signed by : DOD Autorized By Dr. R. Mashayekhi

AHEEEHAPPMLMGAKDMUFELND

HD-IMC-LA-R8--۳--۸۲۸۱۲

تاریخ : ۱۴۰۳/۰۹/۰۳

فرم جوابدهی آزمایشگاه شناسایی و تشخیص بیماری های متابولیک ارثی

نام آزمایش: تاندم نمونه خون خشک شده روی کاغذ از نظر بیماریهای
روش آزمایش: تاندم مس اسپکترومتری
مشخص ساز: SCIEX 3200

کد پذیرش: ۲۲ رقمی کشوری نمونه
-۱۴۰۳-۰۸۳۰-۰۳۴۶-۲۱۰۴۲۸۱۲

نام مادر:
تاریخ نمونه گیری:
تاریخ دریافت نمونه: ۱۴۰۳/۰۸/۳۰
تاریخ پذیرش: ۱۴۰۳/۰۸/۳۰
تاریخ گزارش: ۱۴۰۳/۰۹/۰۳

نام نوزاد: مرسانا غزلی
تاریخ تولد: ۱۴۰۳/۰۶/۱۴
جنسیت نوزاد: زن
مرکز ارسال کننده: Infant ICU
شماره کاغذ گاتری از مرکز بهداشتی: ۲۲۲۲۸

Analyte Abbreviation	Analyte Full name	Result (µM)	reference interval	pathologic border	Description
Ala	Alanine	68.80	<162	>514	Normal
Asp	Aspartic Acid	30.20	<84	>95	Normal
Glu	Glutamic Acid	113.00	<427/00	>461	Normal
Arg	Arginine	1.80	4/00-34	<4 , >42	*
Cit	Citrulline	9.38	5.0-21.0	<4 , >30	Normal
Gly	Glycine	86.00	<417	>486	Normal
Leu+Ile	Leucine+Isoleucine	24.10	<170	>191	Normal
Met	Methionine	5.05	9.0-32	<9 , >36	*
Orn	Ornithine	41.20	<133	>148	Normal
Phe	Phenylalanine	22.80	<69	>112	Normal
Pro	Proline	34.20	<292	>314	Normal
Tyr	Tyrosine	15.80	<264	>303	Normal
Val	Valine	32.20	<156	>166	Normal
C0	Free Carnitine	6.26	8/0-40	<6/5 , >45	*
C2	Acetylcarnitine	6.73	7-38	<5, >40	*
C3	Propionylcarnitine	0.32	0.3-4/6	<0.3 , >5/0	Normal
C3DC & C8OH	Malonylcarnitine & 8-Hydroxyoctanoylcarnitine	0.11	<0/05	>0/15	*
C4	Butyrylcarnitine	0.04	<0.55	>0/75	Normal
C4OH	Hydroxybutyrylcarnitine	0.03	<0.3	>0.5	Normal
C4DC	Methylmalonylcarnitine	0.70	<0/25	>0.34	*
C5	Isovalerylcarnitine	0.03	<0.36	>0.45	Normal
C5DC & C10OH	Glutarylcarnitine & 3-Hydroxydecanoylcarnitine	0.03	<0/15	>0.16	Normal
C5:1	Tiglylcarnitine	0.00	<0.03	>0.09	Normal
C5OH	Hydroxyisovalerylcarnitine	0.05	<0/27	>0.47	Normal
C6	Hexanoylcarnitine	0.01	<0.09	>0.12	Normal
C6DC	Adipoylcarnitine	0.03	<0.05	>0.06	Normal
C8	Octanoylcarnitine	0.01	<0.08	>0.28	Normal
C8:1	Octenoylcarnitine	0.01	<0/18	>0.19	Normal
C10	Decanoylcarnitine	0.01	<0.14	>0.15	Normal
C10:2	Decadienoylcarnitine	0.01	<0.03	>0.05	Normal
C10:1	Decenoylcarnitine	0.03	<0.12	>0.17	Normal
C12	Dodecanoylcarnitine	0.04	<0.3	>0.55	Normal
C12:1	Dodecenoylcarnitine	0.08	<0.2	>0.3	Normal
C14	Tetradecanoylcarnitine	0.03	<0/35	>0.55	Normal
C14:2	Tetradecadienoylcarnitine	0.02	<0.05	>0.08	Normal
C14:1	Tetradecenoylcarnitine	0.01	<0.17	>0.31	Normal
C14OH	Hydroxytetradecanoylcarnitine	0.01	<0/03	>0/04	Normal
C16	Hexadecanoylcarnitine	0.47	0/55-7/08	<0/55 , >8/68	*
C16:1	Hexadecenoylcarnitine	0.03	<0/47	>0.51	Normal
C16:1OH	Hedroxyhexadecenoylcarnitine	0.06	<0/14	>0.15	Normal
C16OH	Hydroxyhexadecanoylcarnitine	0.01	<0.05	>0.14	Normal
C18	Octadecanoylcarnitine	0.38	0.22-1/67	<0.2 , >1.9	Normal
C18:2	Octadecadienoylcarnitine	0.19	0/07-0/68	<0.07 , >0/82	Normal
C18:1	Octadecenoylcarnitine	0.37	0/35-2/5	<0.2 , >2.76	Normal
C18:2OH	Hydroxylinoleoylcarnitine	0.0232	<0/09	>0/1	Normal
C18:1OH	Hydroxyoleoylcarnitine	0.0147	<0/04	>0.05	Normal
C18OH	Hydroxystearoylcarnitine	0.0147	<0/03	>0.05	Normal

Urine Organic Acid Analysis

Growth and Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-03-080048

date:03/09/04

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472414 Fax: 66949662

Patient's name: Mersana Khezli	Lab number:17728	Patient's ID:012030901020418014040048
Sample type: urine	Gender: Female	age:2h,4m,18d
Physician/referred by: CMC	Reception Date: 03/09/01	Reporting date: 03/09/04

Result:

Abnormal Compound	Cut off	measure
Lactic acid	6.70%	13.23%
2-Hydroxyglutaric acid	9.49%	11.35%
3-Hydroxyisobutyric acid	13.02%	13.08%
4-Hydroxyphenyllactic acid	12.51%	46.37%
Pyruvic acid	32.61%	38.06%
Uracil	19.65%	146.96%
3-Hydroxyisovaleric acid	6.10%	12.42%
2-Hydroxyisovaleric acid	0.50%	2.93%
2-Keto-adipic	11.43%	17.00%
Hippuric acid	21.54%	609.14%
4-Hydroxyphenylpyruvic acid	1.90%	3.89%
Fumaric acid	10.36%	24.55%
Butyrylglycine	0.50%	7.10%
2-Hydroxyisobutyric acid	0.50%	1.92%
Malic acid	1.20%	5.79%

Comment:
The urine organic acid analysis shows excretion of small amount of several metabolites that indicate an underlying disease affecting Liver function, as well as vitamins and cofactors insufficiency (including group B and folic acid). Metabolites of Sodium benzoate is also present.

Approved and interpreted by: Dr. Sedigheh shams

Urine Organic Acid Analysis

Growth and Development Research center
Iran Metabolic Center

Document Number: HD-IMC-LA-RS-03-090755

date:03/09/11

Name of Lab Center: Iran Metabolic Center
Address and Telephone Number of Lab Center: Growth and Development Research center Pediatrics Center of Excellence, Children's Medical center ,62 Dr.Qarib St, Keshavarz Blvd, Tehran Telephone 021-61472434 Fax: 66949662

Patient's name: Mersana Khezeli	Lab number:4456	Patient's ID:012030910020416014040755
Sample type: urine	Gender: female	age:2y,4m,16d
Physician/referred by: CMC	Reception Date: 03/09/10	Reporting date: 03/09/11

Result:

Abnormal Compound	Cut off	measure
Uracil	19.65%	106.29%
Orotic acid	2.50%	82.00%

Comment:
The urine organic acid analysis shows increased level of Uracil and Orotic acid, that may indicative urea cycle disorder. Molecular study and clinical correlation is recommended. Lysinuric protein intolerance also should be considered.

Approved and interpreted by: Dr. Sedigheh shams

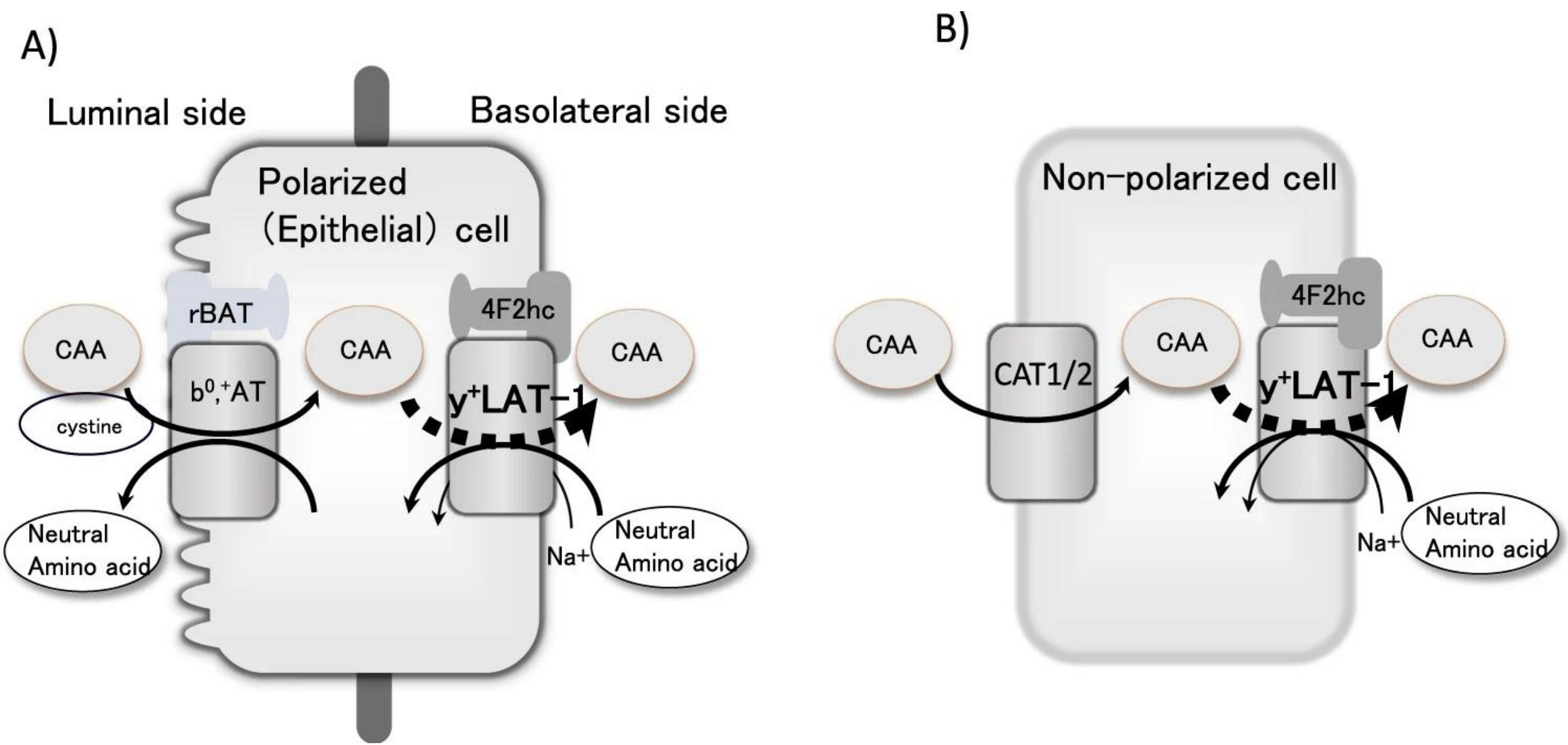
Lysinuric protein intolerance

- dysfunction of the dibasic amino acid membrane transport
- owing to the functional abnormality of y+L amino acid transporter-1
- autosomal recessive inheritance and pathological variants in the responsible gene *SLC7A7*
- transport defect in polarized cells. death, malnutrition, and urea cycle dysfunction
- transport defects in non-polarized cells such as lymphocytes and macrophages have also been recognized as important. renal, pulmonary, and immune disorders

- Over 200 patients have been reported
- in Finland (1 : 50,000)
- Italy ,and Japan , sporadic cases reported worldwide
- estimated 40–45 cases in Japan, with a higher frequency in northern Japan.

Metabolic pathway

- Human y+LAT-1 is a light subunit of heteromeric amino acid transporters. It has a protein structure with 12 transmembrane regions
- This transporter exists mainly on the basolateral membrane of polarized cells, such as those of the kidney and small intestine
- it is responsible for transport of cationic amino acids (CAAs) such as lysine, arginine, and ornithine.



Membranous transport of cationic amino acids(CAA). y+LAT and b0+AT transport both CAA and neutral amino acids. In addition, y+LAT is Na dependent. a CAA transport at an polarized cell. b CAA transport at a non-polarized cell. CAT1/2 (cationic transporter-1/2) are Na+ independent Journal of Human Genetics

- Impairment of intestinal malabsorption and renal tubular reabsorption of CAAs by y^+LAT-1 dysfunction causes
- reduction of these amino acid pools in the body,
- resulting in various symptoms.
- Arginine and ornithine, a part of the dibasic amino acids, are also substrates for the urea cycle.
- These deficiencies may lead to dysfunction of the urea cycle and cause hyperammonemia, but details are unknown.

- l-arginine is a precursor substance of endogenous nitric oxide (NO) synthesis.
- impaired regulation of CAA intra-extracellular transport due to dysfunction of y+LAT-1 may result in :
- an increase in intracellular arginine, inducing intracellular NO accumulation.
- It is involved in the complex pathology such as:
- dysfunction of the immune, bone metabolism, kidney, and lung systems.

- Kamada et al reported:
- the functional impairment of vascular endothelial cells in patients with LPI associated with arginine deficiency.
- In detail, myocardial ischemic change in positron emission tomography was improved by arginine administration and presumed to be due to a decrease in serum NO .
- Takeda et al. evaluated portal flow in seven patients and reported a decline in portal circulation as a result of l-arginine deficiency.

Physical features

- After weaning,
- short stature (limb/trunk equilibrium type)
- low body weight
- Infants are often referred to hospitals for consultation related to poor weight gain, hepatosplenomegaly, and short stature.
- Occasionally, hepatosplenomegaly can be identified in the neonatal period.
- Some patients with short stature also have complicated growth hormone (GH) deficiencies .
- Recurrent fractures occur frequently and may indicate bone disease .
- The rate of osteoporosis is high and severe from childhood to adulthood .
- Sometimes, a delay in bone maturation, bone deformity, and osteoarthritis are also recognized.
- In addition, sparse hair growth, loose skin, and excessive extension of joints may be observed.

Hyperammonemia/neurological symptoms

- After excessive protein intake, discomfort, behavioral changes, and loss of consciousness occur due to hyperammonemia.
- recurrent episodic mild encephalopathy .
- Starvation, infection, and stress can trigger hyperammonemia
- However, some patients do not display consistent symptoms of hyperammonemia.
- Instead, they often show transient hyperammonemia only after meals (after protein loading), resulting in difficult diagnosis of this disorder. Therefore:
- diagnosis may be delayed into adulthood.

Gastrointestinal symptoms

- After excessive intake of protein-rich foods, patients display:
- nausea, vomiting, abdominal pain, and diarrhea.
- Generally, gastrointestinal symptoms occur after weaning at ~1 year
- and patients develop an extreme dislike of these foods.
- Protein aversion is a characteristic feature of this disease and is present in about 80% of patients.

Immune abnormality, autoimmune disease, and blood cell phagocytosis syndrome

- Aggravated viral infections are frequently shown in LPI patients.
- It has been reported that patients with LPI had :
- severe varicella infection
- combined with severe interstitial pneumonitis,
- hepatitis,
- decreased platelet count,
- bleeding, and elevated serum lactate dehydrogenase (LDH)/ferritin levels .
- Other viral infections (measles encephalitis, and Epstein-Barr virus infection)
- low levels of leukocyte phagocytic, cytotoxic, and natural killer (NK) cell activity
- increased spontaneous proliferation of lymphocytes
- In these cases, although a vaccine is useful, it can be difficult to acquire antibodies .

- hemophagocytic syndrome
- autoimmune disease (systemic lupus erythematosus with antinuclear antibodies)
- autoimmune hepatitis, and :
- rheumatoid arthritis
- In metabolome analysis of molecular lipids and polar metabolites derived from patients, it was suggested that:
- amino acid imbalance affected the Tricarboxylic acid (TCA) cycle, β-oxidation, lipid metabolism, oxidative stress, and apoptosis .

Renal involvement

- Renal disease is a frequent and progressive complication in LPI
- In many patients, mild proteinuria and microhematuria are observed.
- Sometimes the initial symptom observed may be only mild proteinuria .
- serum creatinine increase.
- Glomerulonephritis has also been often reported

- These findings are frequently observed in adulthood (from childhood in some patients) and are slowly progressive
- Renal histological findings are heterogeneous from tubulointestinal disorder to distinct glomerulonephritis, often showing membranous or mesangial proliferative glomerulonephritis

.

- There is a necropsy report of glomerulonephritis with IgA deposition
- renal tubular acidosis and Fanconi syndrome may also accompany LPI and require appropriate treatment.
- Urinary β-2 microglobulin was elevated in 90% of LPI cases, suggesting an early marker of renal involvement and indicating that regular monitoring of this marker is beneficial
- Some cases ultimately lead to renal failure ; therefore, caution is needed for treatment and observation of renal function.

- end-stage renal failure associated with LPI,
- awareness of potential osteoporosis and carnitine deficiency should also be considered

Lung involvement

- Respiratory disease is a serious complication affecting prognosis.
- Pulmonary complications include:
- interstitial pneumonia and pulmonary alveolar proteinosis .
- Although asymptomatic in early stages, interstitial lesions are seen in chest X-rays and can also be observed by chest high-resolution computed tomography
- Diffuse reticular nodular stromal shadows are characteristically seen in the chest X-ray or HRCT over time.

- pulmonary involvement in 10 out of 14 children with LPI. Five of them had acute symptoms. HRCT was conducted in seven cases and interstitial lesions were observed in all cases, and fibrosis in four cases . also observed PAP in 10 out of 16 patients during 11 years of follow-up in France, and half of the patients had pulmonary fibrosis.

- In bronchoalveolar lavage with PAP, an increase in the number of cells and foamy macrophages are observed.
- Lung biopsy of LPI patients may show cholesterol granulomas and/or alveolar proteinosis. Alveolar proteinosis can progress rapidly and become life-threatening, which is considered typical of terminal-stage pulmonary complications
- . Respiratory symptoms may occur at any age and be the initial symptoms in new patients. Even if standard treatment has been introduced, symptoms may proceed on a monthly or yearly base
- The exact cause of PAP is unknown; however, intracellular accumulation of NO may be related to the occurrence of PAP

Liver involvement

- Hepatomegaly in infancy is recognized in about 70% of patients
- . However, elevation of serum transaminase is mild and often aspartate aminotransferase (AST) dominant.
- Jaundice and cholestasis are rarely observed, except in progressive liver cirrhosis.
- Steatosis is observed in many cases, although there are not many findings on LPI liver pathology.
- It is speculated that symptoms are caused by protein malnutrition.
- Generally, the liver of Kwashiorkor patients shows increased steatogenesis and apolipoprotein synthesis, as well as inhibition of lipoprotein lipase activity.
- In Kwashiorkor, lipid droplet deposition first appears in the hepatic portal area, not around the central vein, a process similarly observed in LPI, suggesting that low protein intake by the patient will result in similar symptoms to Kwashiorkor.

- . Steatosis and fibrosis of portal areas are also seen in urea cycle disorders such as ornithine transcarbamylase deficiency, carbamyl phosphate synthase deficiency, and hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. These diseases are common in metabolic dysfunctions related to arginine and citrulline;

- These findings represent various stages of slowly progressive pathological results.
- Pathology is assumed to begin with the deposition of lipid droplets and inflammation of the portal area, but gradually bridging fibrosis becomes apparent, and finally progresses to diffuse cirrhosis. In LPI, impairment of the urea cycle, portal circulation disorder due to NO decline due to arginine deficiency and immune abnormality are also considered to contribute to liver damage.

Other symptoms

- There are few reported cases of cardiovascular symptoms.
- Myocardial ischemic change after exercise
- myocardial infarction, and sinus arrest requiring a pace-maker are reported.
- Vascular lesions (cerebral infarction) thought to be based on vascular endothelial dysfunction have been observed,
- Acute pancreatitis is also occasionally observed, although the association with hyperlipidemia is unknown.

Laboratory findings

- General blood examinations
- Serum LDH usually increase to 600–1000 IU/L
- serum ferritin value varies.
- Most cases have episodes of hyperammonemia.
- . In newborns and infants, values of >120 µmol/L (200 µg/dL) and >60 µmol/L (100 µg/dL) have been reported, respectively.
- In some cases, transient hyperammonemia is detected
- Approximately one-third of patients have some hematological abnormalities (leukocytopenia, thrombocytopenia, and anemia).
- Peripheral blood counts include normochromic or hypochromic anemia, leukopenia, thrombocytopenia, and latent intravascular coagulopathy.
- Bone marrow aspiration shows megakaryocyte reduction and erythroblast phagocytosis.
- In a study of coagulability, defective primary hemostasis, fibrin abnormality, and other deficiencies are detected

- High levels of serum total cholesterol/triglyceride and low levels of high-density lipoprotein have also been reported
- The precise causes of hyperlipidemia are not yet known
- Insulin-like growth factor-1 (IGF-1) values of LPI are low
- Only some individuals exhibit GH deficiency .
- The exact pathophysiology of GH deficiency is unknown
- amino acids such as arginine and lysine can stimulate GH secretion. Some patients respond to GH treatment for short stature due to GH deficiency, suggesting the GH/IGF-1 axis should be investigated in LPI
- . In addition, slight increases in AST/alanine aminotransferase (ALT) (AST > ALT), thyroid-binding protein increases, deficient B-cell functions, low concentrations of immunoglobulin G subclasses
- hypergammaglobulinemia, decreased leukocyte phagocytosis, decreased fungicidal activity, decreased NK cell activity, hypocomplementemia, and decreases in the CD4/CD8 ratio may be observed.

Amino acid analysis in blood/urine

- Blood concentrations of dibasic amino acids (lysine, arginine, and ornithine) are distributed from about one-third of normal to the lower limit of the normal range
- . As a secondary change, blood glutamine, alanine, glycine, serine, and proline levels tend to be elevated. Glutamine levels reflects hyperammonemia and are often elevated 800–1200 nmol / mL
- Urine concentration of dibasic amino acids usually increases (lysine shows the largest increase, arginine and ornithine increases are moderate, and cysteine increases are mild), in almost all cases.
- Blood and urine amino acid analyses are important during diagnosis, but under malnutritive conditions the overall blood amino acid level is low and urinary excretion may also be reduced.
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- In newborns and premature infants, excretion of amino acids in urine is excessive. Furthermore, under administration of amino acids and in Fanconi syndrome, excessive excretion of urinary amino acids occurs. Clinicians should carefully evaluate levels of amino acids in neonatal urine.

- In some cases, it may be necessary to calculate the renal clearance of these amino acids
- . In urinary organic acid analysis, urinary orotic acid is increased, accompanied by hyperammonemia.

Treatment
Acute phase treatment

- 1) Glucose infusion
- 2) Drug administration:

  l-arginine (100–250 mg/kg/day, iv)

  If l-arginine is not sufficiently effective,

  sodium phenylbutyrate (450–600 mg/kg/day in patients weighing

  <20 kg, or 9.9–13.0 g/m2/day in larger patients), and/or;

  sodium benzoate (100–250 mg/kg/day)

These drugs can be used alone or in combination, depending on each situations.

3) Blood purification

Chronic phase treatment

- Diet therapy:
- 0.8 (1.0)−1.5 g/kg/day protein intake is recommended for children and 0.5–0.8 g/kg/day for adults
- citrulline administration
- Calcium and vitamin D
- iron and zinc
- Inclusion of special medical foods (e.g., low protein foods, protein-free milk) should also be considered.

Pharmacotherapy

- l-citrulline (~100 mg/kg/day) By administering l-citrulline,
- decreases in blood ammonia level,
- increases in dietary intake,
- increases in daily life activity,
- and reduction of hepatomegaly are observed.
- l-Arginine (Argi U® 120–380 mg/kg/day) administration is controversial
- l-carnitine (20–50 mg/kg/day)
- l-lysine (20–50 mg/kg/day)

- lung lavage
- For nephritis, angiotensin-converting enzyme blocker corticosteroids and mycophenolates are used. Some cases require treatment, such as lupus nephritis.
- Vaccinations
- Bone marrow transplantation
- renal transplantation for end-stage renal failure