Diagnosis and treatment of disorders of amino acid metabolism in autism

Y.B. Grechanina

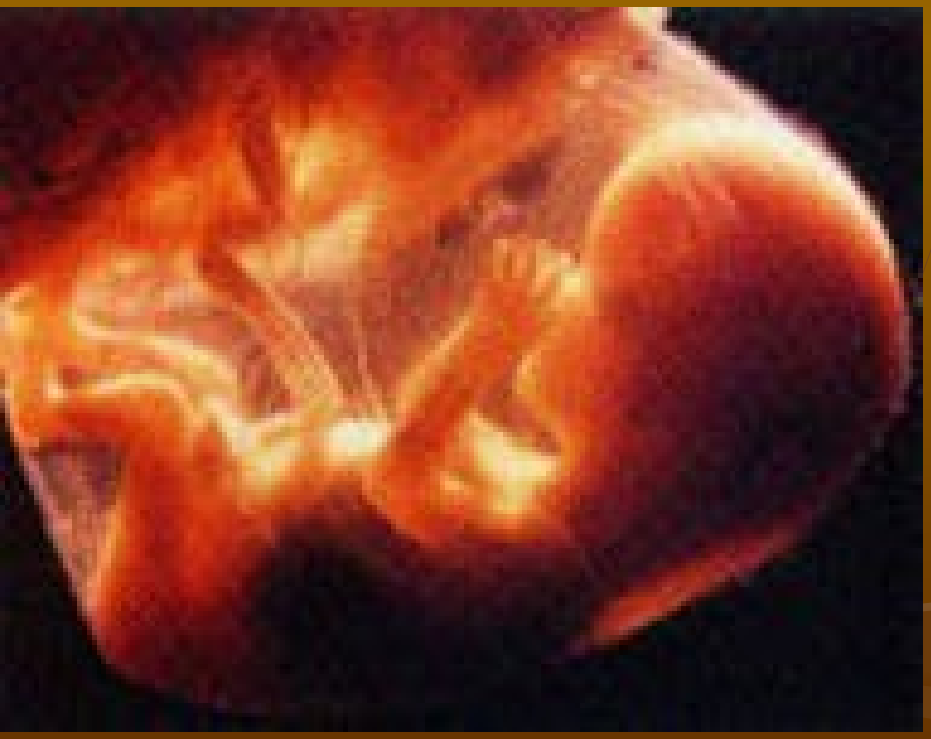
«IF A DRUG FITS TO EVERYBODY, IT MEANS IT DOESN'T FIT TO ANYBODY».

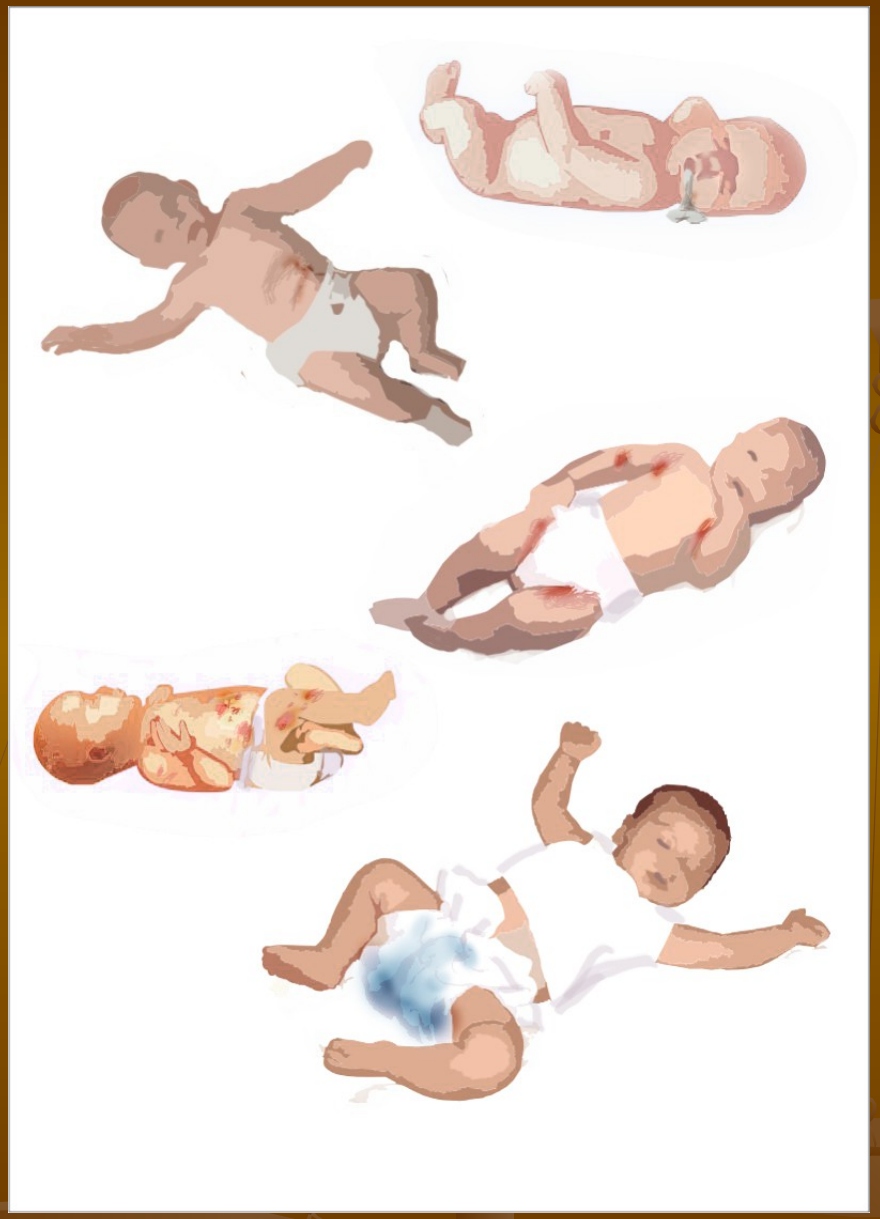
When AUTISM and autistic features of behavior have the metabolic base – this, on the one hand, worsens course severity, on the other hand – gives the concrete direction of the treatment .

Since a human began to intervene into actions of a natural selection, it has to change levels of its influence turning one stage of ontogenesis to another.

Attempts of saving interruptive in early terms of a pregnancy with the help of medicines lead to pretended victory – the frequency of birth of children with the inborn and inherent pathology by our data increases 4 times. (E.Y. Grechanina, 2012)

Signs of metabolic disorders we can observe already prenatally and in the newborn period





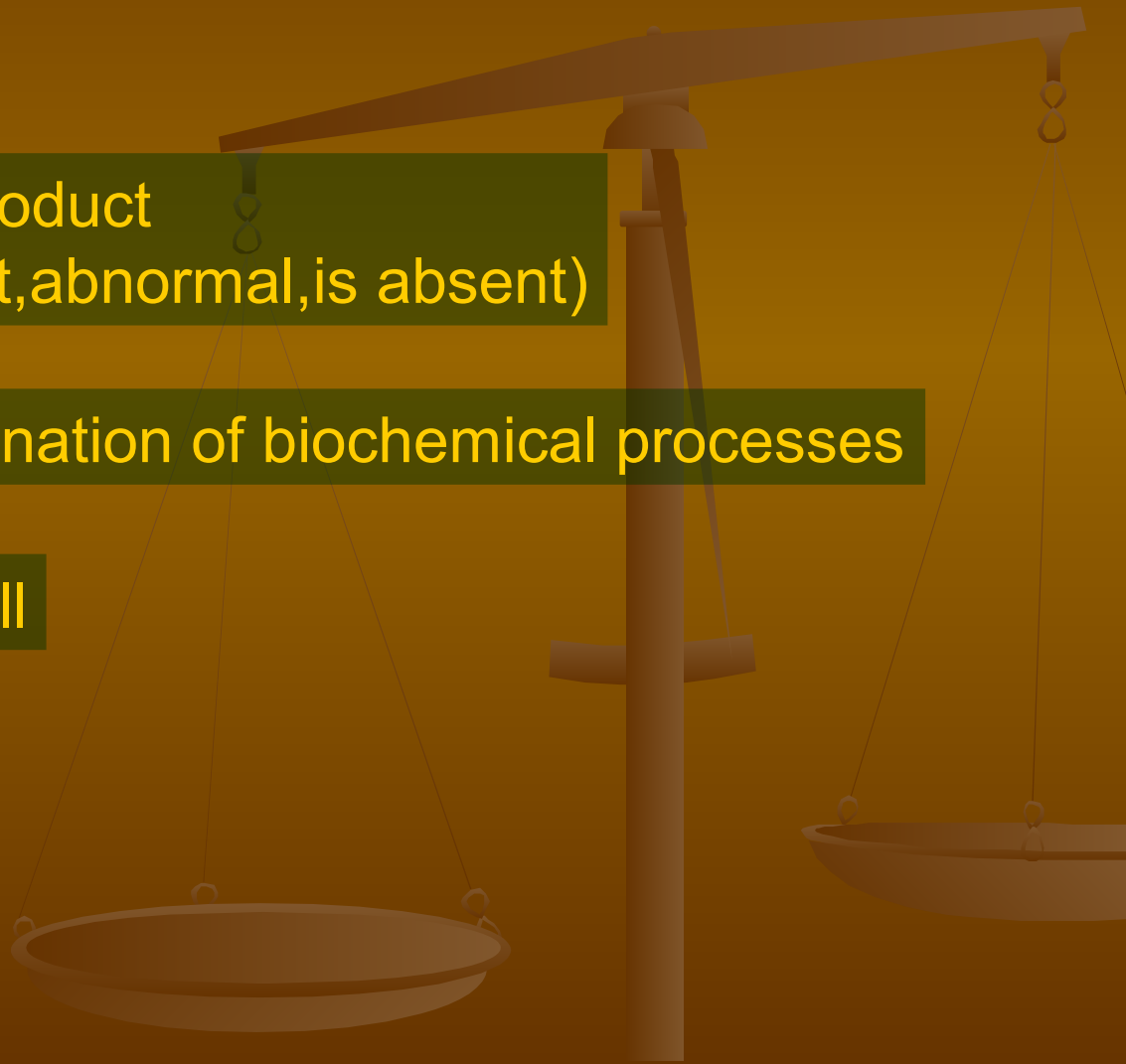
Urine color

Color	Compound	Disorder, the source of disorders
Blue	Indican	blue diaper syndrome
Brown-blue	Homogentisic acid	Alcoptunuria
Brown	Methemoglobin	Myoglobinuria
Brown-red	Hemoglobin/ methemoglobin	Hemoglobinuria
Red	Erythrocytes	Hematuria
Red	Porphyrines	Porphyry
Red	Pyrosolons	Medicines
Red	Phenolphthalein	Chemical substances
Light red	Urats	Physiological, hyperuricosuria
Red	Beet	Caused by feeding
Yellow	Riboflavin	Vitamins

Urine odor

Musty, mouse	Phenylacetic	Classical PKU
Maple syrup, burnt sugar	2- Oxoisocanronic acid 2-Oxo-3-methylvaleric acid	«Maple syrup» disease (MSUD)
Sweaty legs	Isolaleric acid	Isolaleric acidemia. 3-oxi-3-methylglutaric aciduria, multiple defects of acyl-CoA-dehydrogeneration (MAD)
Cat urine	3-Oxiisovaleric acid	3-Methylcrotonylglicinuria, multiple deficiency of carboxylase
Cabbage	2-Oxibutyric acid	Malabsorption of methionine, Tyrosinemia 1
Spoiled oil	2-Oxo-4-methylbutyric acid	Tyrosenemia 1
Acid	Methylmalonic acid	Methylmalonic aciduria
Sulfur	Hydrogen sulfide	Cystinuria
Fish	Trimethylamine	Trimethylaminuria

Pathogenesis of metabolic diseases: can be manifested symptomatically



Mutant allele

↓

Pathologic primary product
(excessive,insufficient,abnormal,is absent)

↓

Disorder of the combination of biochemical processes

↓

Pathology inside a cell

↓

Pathology of organs

↓

Pathology of
the body

Obstetrical anamnesis in metabolic diseases

- Spontaneous abortion or deadborn in the anamnesis should be considered as elimination of an unviable child.
-Male gender of such fetus can say about X-linked form of metabolic diseases;

-The presence of pathologic changes in a pregnant, such as continued toxicosis or an acute fatty dystrophy of the liver, can be the result of the disorder of fatty acid oxidation in a fetus.

Mechanisms of the onset of metabolic crisis in IMD

(по Johannes Zschocke, Georg F. Hoffmann, 1999)

Mechanisms of onset	Disorder groups
Fasting, infections, fever, operations, traumas	Disorder of metabolism of proteins, hydrogens, energy metabolism
Consumption of the high amount of protein and/or protein catabolism	Disorder of protein metabolism: aminoacidemias, organic acidurias, defects of urea cycle
Change during hydrogen consumption	Mitochondriopathies
Quickly absorbed	Hyperinsulinism, mitochondriopathies

Mechanisms of the onset of metabolic crisis in IMD

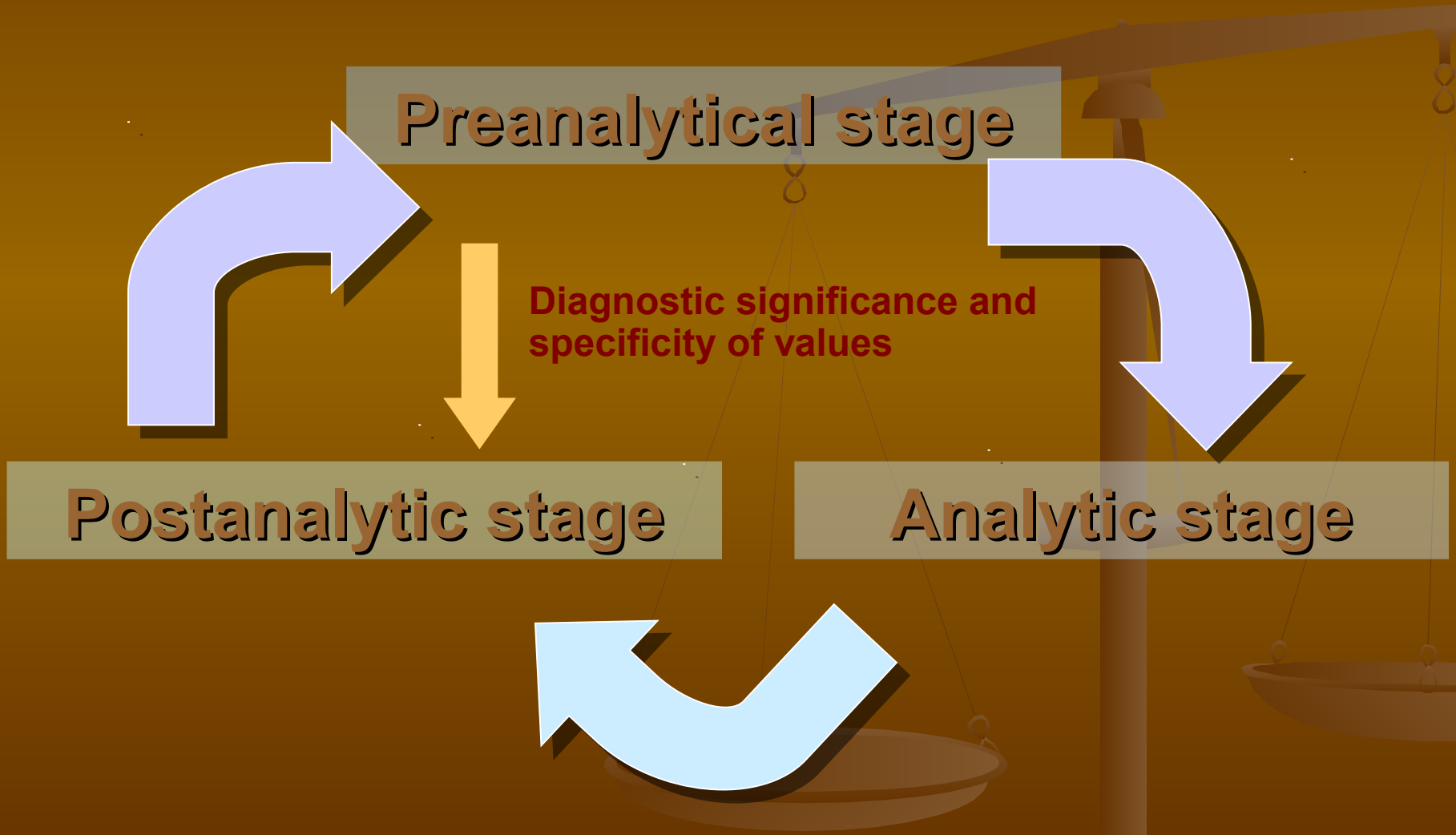
(по Johannes Zschocke, Georg F. Hoffmann, 1999)

Fruit, table sugar (sucrose)	**fructose intolerance**
Lactose, milk products	**Galactosemia**
Consumption of the high amount of fats	**Disorder of fatty acid oxidation, lipoprotein lipase deficiency, glycerol kinase deficiency , glycerin intolerance**
Medicines	**Porphyrias, glucose-6-phosphat-dehydrogenase deficiency, disorder of fatty acid oxidation**

When it is necessary to suspect metabolism disorder?

- Lethargy
- Refuse from food
- weight loose
- breath disturbance
- hypothermia
- hypotonia
- unusual motions
- hepatomegaly
- convulsions
- polyorgan changes
- coma

Stages of laboratory study



Preanalytical stage:

- Somatic and genetic study
- syndromologic, clinical and genealogical analysis
- Preparation of a patient for the study
- Sampling of the biochemical material
- Preservation and transport of samples

Organic acids – low molecular compounds, which are products metabolism of amino acids, hydrogen, lipids, biogenic amines.

Organic acidurias (acidemias) – a group of inherent diseases, which is characterized by the disorder of intermediate metabolism with the accumulation of carboxyl acids. Toxic compounds disturb intercellular metabolic pathways, including glucose catabolism (glycolysis), glucose synthesis (gluconeogenesis), metabolism of amino acids and pyrimidines and also fats .

Types of organic acids (OA)

- ***OA, caused by the deficiency of enzymes participating in transformation of amino acids (leucine, isoleucine, valine, lysine, tyrosine, aminobyturic acid).***
- ***OA, caused by the disorder of bioenergy processes (Creb's cycle), cellular breath, oxidative phosphorylation in mitochondria of cells.***
- ***OA, caused by the disorder of transport or mitochondrial oxidation of fatty acids.***

1 group- clinical manifestations:

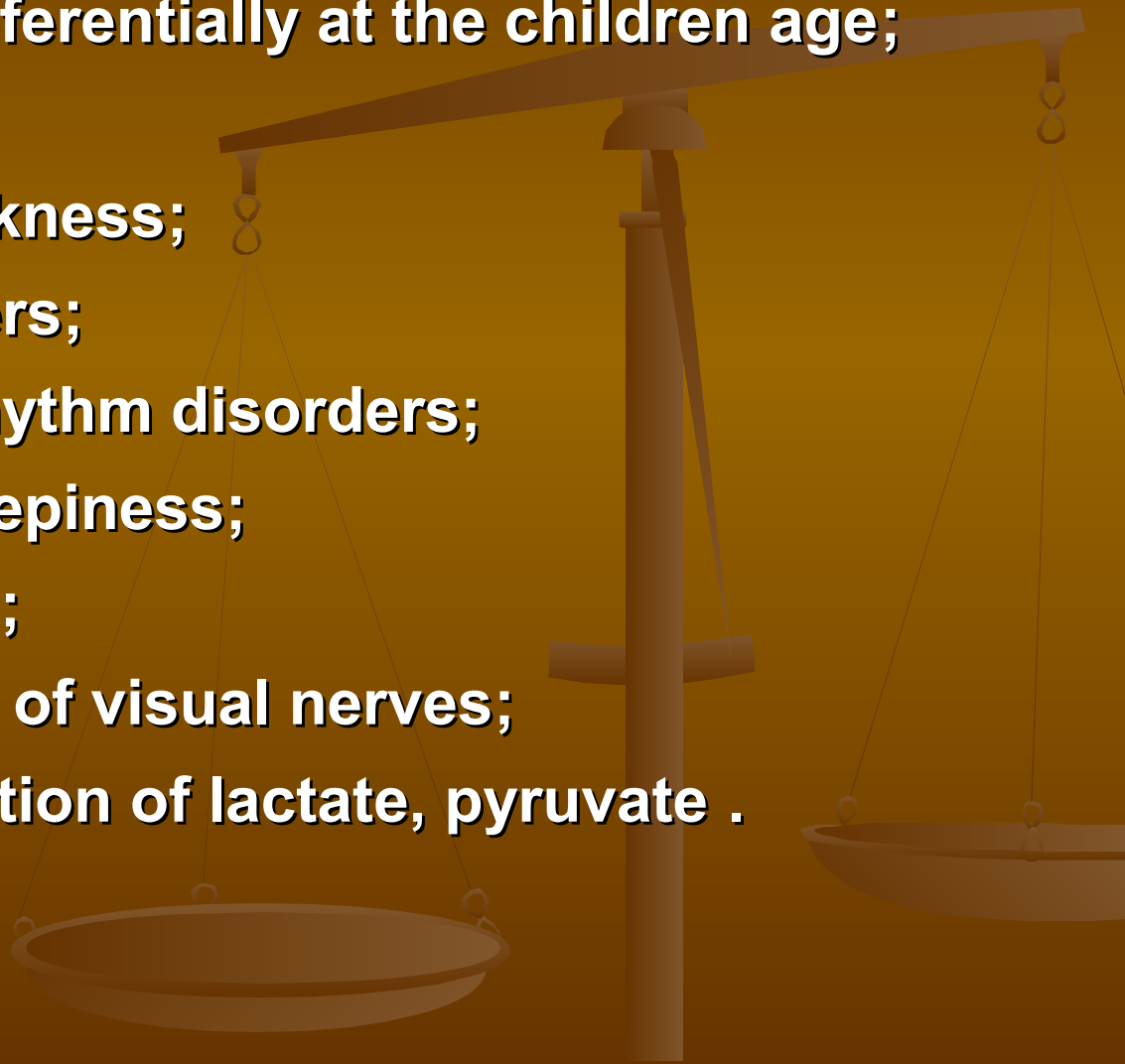
Manifestation

(or at the early age)

- **acute onset**
- **convulsions**
- **apnoe, dyspnea**
- **increased irritation (or inhibition) of CNS**
- **muscle hypotonia**
- **anorexia**
- **vomiting**
- **sometimes extrapyramidal disorders**

2 group – clinical manifestations:

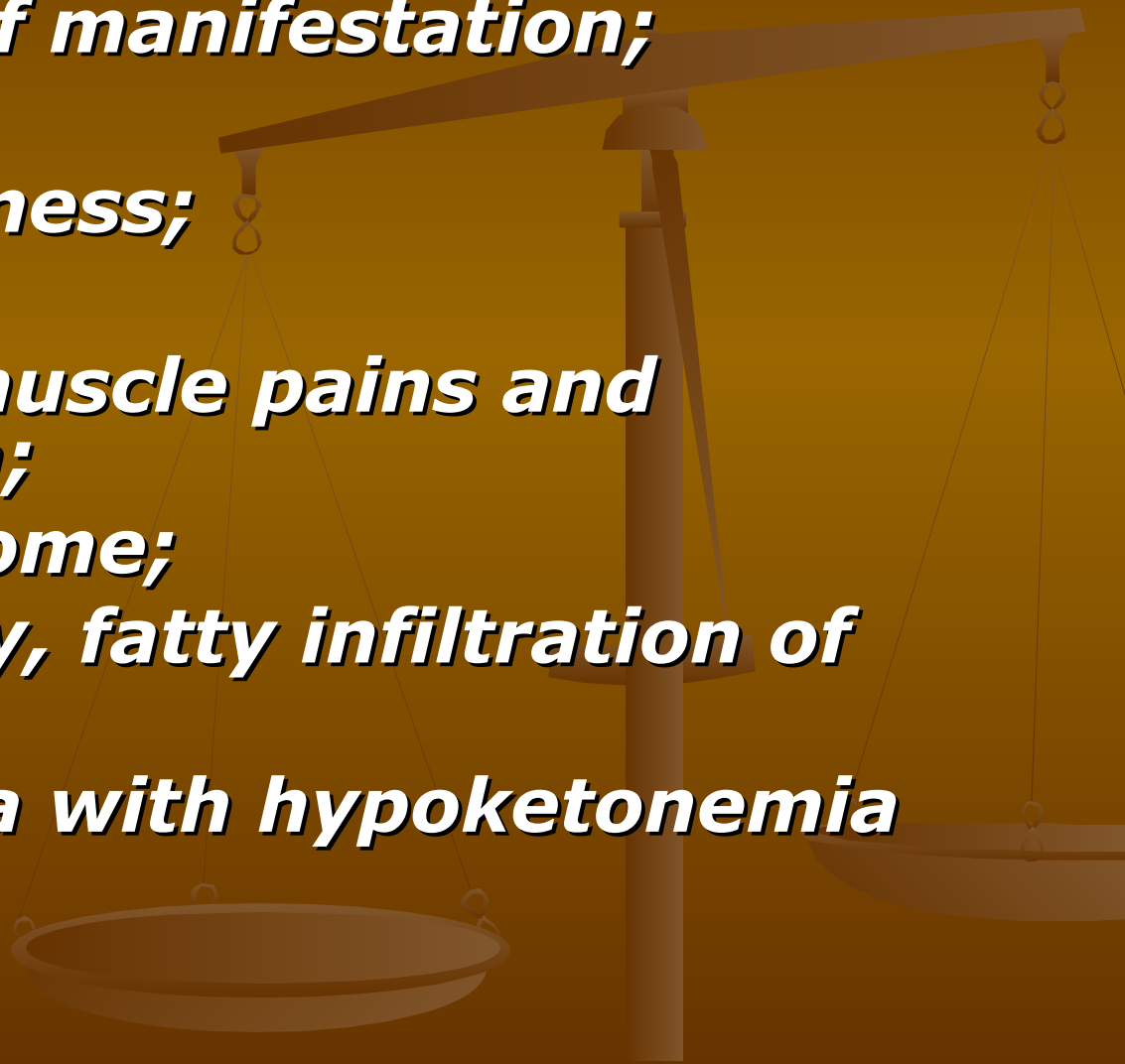
- Manifestation is preferentially at the children age;
- Development delay;
- Abrupt muscle weakness;
- Respiratory disorders;
- Cardiomyopathy, rhythm disorders;
- Nervousness or sleepiness;
- Convulsions, ataxia;
- Nistagmus, atrophy of visual nerves;
- Acidosis, accumulation of lactate, pyruvate .



3 group – clinical manifestation:

Different time of manifestation;

- *vomiting;*
- *muscle weakness;*
- *hypotonia;*
- *episodes of muscle pains and myoglobinuria;*
- *Reye's syndrome;*
- *hepatomegaly, fatty infiltration of the liver;*
- *hypoglycemia with hypoketonemia*



Specialised Medical Genetic Centre. Kharkiv, Ukraine.

Organic acids analysis

PATIENT DATA

Sample Num	133
Registr	06.02.2012
Patient(FIO)	Borisyuk I.V
Gender m	Age 47
Doctor(FIO)	E.Ya.Grechanina, Molodan L.V.
Gen card	
Diagnosis	obsledovanie

PRERUN RESEARCH

compound	result	norm range	compound	result	norm range
Krea level, mmol/L	23.89		Bilirubin, mg/dl	otr	negative
Reduction Probe	sledi ↑	negative	Urobilinogen, mg/dl	N	negative
Ketoacid	otr	negative	pH	6.0	5,0-7,0
Lejcinoz test	otr	negative	Specific Gravity	1.030	1,005-1,030
Cistine	otr	negative	Blood, mg/dl	+0.09 ↑	negative
Sulfit test, mg/l	otr	negative	Ketone, mg/dl	otr	negative
Glucouse, mg/dl	N	normal	Nitrits	otr	negative
Protein, mg/dl	+-15 ↑	negative	Leucocites, Leu/ul	otr	negative

RESULT OF QUANTITY ORGANIC ACIDS ANALYSIS

Name of organic acids	Result (mmol/mol crea)	Reference value (mmol/mol crea)	Name of organic acids	Result (mmol/mol crea)	Reference value (mmol/mol crea)	Name of organic acids	Result (mmol/mol crea)	Reference value (mmol/mol crea)
Lactic:	4.75	2.09 - 31.52	Uracil*:	0.2		Tartaric:	n.d.	n.d.
Glycolic:	53.61	8.3 - 138.26	Glyceric:	n.d.	n.d.	Suberic*:	0.24	0 - 2.9
2-Hydroxybutyric:	0.22 ↑	0 - 0.20	Fumaric*:	0.03 ↓	0.2 - 0.8	n-Acetyl-L-aspartic*:	n.d.	
Oxalic:	16.05 ↓	18.59 - 198.52	Glutaric:	n.d.	n.d	Orotic*:	n.d.	n.d
3-Hydroxybutyric:	n.d.	n.d.	Thymine:	n.d.		Azelaic*:	0.36 ↓	1.3 - 15
Malonic:	n.d.	n.d.	3-methylglutaric:	n.d.	0 - 1.01	Citric:	107.43	11.95 - 377.6
Methylmalonic:	present	0 - 1.41	D-malic:	n.d.	0 - 6.21	Isocitric:	15.33	3.53 - 53.92
Glycerol:	n.d.	0 - 469.43	Adipic:	0.12	0 - 7.90	N-acetyltirosine:	n.d.	n.d.
Benzoic*:	n.d.	1.9 - 6.5	5-Oxoproline:	13.84	1.20 - 21.89	Succynylacetone	n.d.	n.d.
Maleic:	n.d.	n.d.	3-methyladipic:	0.69	0 - 3.22			
Succinic:	0.38	0.34 - 20.81	Pimelic:	0.11	0 - 0.96			

RESULT OF SEMIQUANT ORGANIC ACIDS ANALYSIS

Compounds name	Result	norm U/mol Crea
Hydroxyisobutyric acid:	6.2	0.72 - 12.69
Caproic acid:	0.8	
Levulinic acid:	14.4	
3-hydroxypropionic acid:	n.d.	
Cresol:	34.6	0 - 384.12
3-Hydroxyisobutyric acid:	4.2	0.75 - 7.33
Erythronilic acid:	21.2	0.17 - 60.47
2-Hydroxyisovaleric acid:	2	0 - 22.89
2-Ethylhydracrylic acid:	3.8	0.79 - 16.69
Urea:	583.8	0.66 - 1188.61
Acetoacetic acid:	n.d.	0 - 31.15
Caprilic acid:	n.d.	
Phosphoric acid:	1.8	0 - 478.19
Ethylmalonic acid:	1.8	0.50 - 7.97
Methylsuccinic acid:	0.4	0.15 - 1.74
3hydroxy-n-valeric:	n.d.	0 - 0.23
Pelargonic acid:	1.4 ↓	2.43 - 60.96
5 hydroxyhexanoic:	n.d.	
4-deoxythreonic acid:	107.8	11.21 - 141.95
Phenoxyacetic acid:	n.d.	0 - 18.02
3-Methylglutaconic acid:	1 ↓	2.14 - 20.48
3,4-Dihydroxybutiric acid:	5.2	1.00 - 16.92
4 hydroxycyclohexylcarboxyli	n.d.	0 - 14.97
Sumiki's:	15	3.44 - 133.51
2-hydroxyphenylacetic acetic:	0.4	
2-hydroxyglutaric:	0.8	0 - 4.16
3-Hydroxyphenylacetic acid:	88.4	3.16 - 164.31
3-hydroxymethylglutaric:	n.d. ↓	0.21 - 5.18

Compounds name	Result	norm U/mol Crea
Oxoglutaric acid:	n.d. ↓	3.16 - 57.85
4-hydroxybenzoic acid:	17	0 - 40.92
p-hydroxyphenylacetic acid:	47.8	14.77 - 175.08
2,5 furandicarboxylic acid:	n.d. ↓	9.23 - 344.78
Furoylglicine:	0.8	n.d
Isocitric lactone:	n.d.	0 - 34.53
Aconitic acid:	1.8	0.51 - 17.37
Vanillic acid:	n.d.	n.d.
Homovanillic acid:	15.4 ↓	20.05 - 101.34
Gentisic acid:	6.8	3.66 - 131.32
p-hydroxymandelic acid:	57	
Hippuric acid:	3005 ↑	94.31 - 2046.05
3-(3Hydroxyphenyl)-3-hydroxypropionic acid:	6.6	1.08 - 42.13
Isohomovanillic acid:	69.4 ↓	72.02 - 269.51
Hydroxyphenyllactic acid:	2.2	2.08 - 29.76
Indoleacetic acid:	14.8	8.83 - 223.76
3-methoxy-4-hydroxyphenyl-3-hydroxypropionic acid:	13.6	6.29 - 310.10
Palmitic acid:	139.6	36.37 - 402.39
Salicyluric acid:	n.d.	0 - 55.58
3-hydroxysebacic acid:	n.d.	0 - 3.24
3-hydroxyhippuric acid:	n.d.	0 - 6.64
linoleic acid:	1.8	0 - 27.37
Oleic acid:	22.2	7.10 - 73.61
p-hydroxyhippuric acid:	n.d.	0 - 441.29
5-Hydroxyindoleacetic acid:	22	0 - 223.43
Stearic acid:	53.2	30.23 - 345.18
Hydroxyproline dipeptid:	n.d.	0 - 248.50

Date: "07" 02 2012

Signature: Гречина, Каменка

Харьковский Специализированный Медико-Генетический Центр, Украина

Исследование органических кислот мочи

ФИО Пациента	[redacted]	Возраст	11м	Регистрационный №	543
ФИО Врача	доц. Гречанина Ю.Б.	Пол	м	Дата приема	08.04.2013
Диагноз	СТД			Генетическая карта	2013

Предварительные исследования

Вещество	Результат	Норма	Вещество	Результат	Норма
Креатинин, ммоль/л	7.62 ↑	0,71 - 5,6	pH	5.0	5,0-7,0
Кетокислоты	отр.	отсутствуют	Удельная Плотность	>1.030 ↑	1,005-1,030
Глюкоза, мг/дл	N	N (норма)	Кровь, мг/дл	отр.	отсутствует
Белок, мг/дл	++100 ↑	отсутствует	Кетоны, мг/дл	отр.	отсутствуют
Билирубин, мг/дл	отр.	отсутствует	Нитриты	отр.	отсутствуют
Уробилиноген, мг/дл	N	N (норма)	Лейкоциты, Leu/µl	отр.	отсутствуют

Вещество	Состоит в группе(ах)	Результат		Норма	
1. Метаболиты цикла Кребса и состояния активности ферментов дыхательной цепи					
Citric	11,14	31.53		25.7 - 648.57	mmol/mol KREA
Aconitic	2, 11, 13, 14	10.47		0 - 35.51	Umol/mmol KREA
Isocitric	12, 13, 14	56.8		5.7 - 133.99	mmol/mol KREA
Oxoglutaric	7, 9, 11, 12, 13, 14	182.72		0 - 677.2	Umol/mmol KREA
Succinic	2, 11, 12, 13	2.78		2.51 - 127.6	mmol/mol KREA
Fumaric	7, 11, 12	6.02		1.2 - 25.25	mmol/mol KREA
Malic	7, 12	n.d.		0 - 47.26	mmol/mol KREA
2-hydroxyglutaric (см. Oxoglutaric)	7, 9, 11, 12, 13, 14	33.09	↑	0 - 18.88	Umol/mmol KREA
Malonic (липогенез, угнетение ферментов цикла)		n.d.		n.d.	mmol/mol KREA
Methylmaleic (угнетение ферментов цикла)	7	1.76		0 - 1.92	Umol/mmol KREA
Tartaric (угнетение ферментов цикла)	7, 9, 17	n.d.		n.d.	mmol/mol KREA
Lactic	5, 8, 12, 13	41.13		6.32 - 142.49	mmol/mol KREA
Pyruvic	5, 12, 14	present		-	Umol/mmol KREA
Tyglylglycine	2, 11	21.93	↑	n.d.	Umol/mmol KREA
3-hydroxymethylglutaric	7, 11, 12	14.18		0 - 33.1	Umol/mmol KREA
2. Метаболиты обмена серы: индикаторы активности витаминов B12 и фолиевой кислоты; недостаточности Молибдена (Mo); индикаторы Цистеина (Cys), метионина (Met), нарушения процессов метилирования					
Сульфиды (Mo, метаболизм серы)	17	100	↑	отсутствуют	мг/л
Проба на цистин		отр.		отрицательная	-
Methylmalonic (B12)		n.d.		0 - 8.24	mmol/mol KREA
↓ Vanilmandelic (нарушения процессов метилирования, Mo)	10, 12, 13	1031	↑	0 - 778.6	Umol/mmol KREA
↓ *Homovanilic* (нарушения процессов метилирования)	10, 12, 13	119.03		0 - 365.66	Umol/mmol KREA
Uracil (фолиевая кислота)	5, 6	6.29		0 - 10.87	mmol/mol KREA
Tyglylglycine (Met)	1, 11	21.93	↑	n.d.	Umol/mmol KREA
Succinic (Met)	1, 11, 12, 13	2.78		2.51 - 127.6	mmol/mol KREA
3-hydroxypropionic (B12)	8, 12, 13, 15	13.32		0 - 24.66	Umol/mmol KREA
Ethylmalonic (B12)	4, 12	5.16		0 - 18.49	Umol/mmol KREA
3-Hydroxybutyric (B12)	4	13.57	↑	n.d.	mmol/mol KREA
Acetoacetic (B12)	4	5.06		0 - 29.58	Umol/mmol KREA
5-Oxoproline (Cys)	8, 9, 13, 14, 15	116.5	↑	15.82 - 74.46	Umol/mmol KREA
Aconitic (Cys)	1, 11, 13, 14	10.47		0 - 35.51	Umol/mmol KREA
Thiodiacetic				-	Umol/mmol KREA
3. Метаболиты оксалатов					
Oxalic	12	41.67		30.05 - 219.8	mmol/mol KREA
Glycolic	8, 12	52.91		10.79 - 607.58	mmol/mol KREA
Glyceric	8, 12	n.d.		n.d.	mmol/mol KREA

4. Кетоновые тела, метаболиты окисления жирных кислот				
Кетоны		отр.		отсутствуют
3-Hydroxybutyric	2	13.57	↑	n.d.
Acetoacetic	2	5.06		0 - 29.58
Adipic	12	7.98		0 - 36.92
Suberic	12	0.2		0 - 9.6
Sebacic				-
Pimelic	11, 17	0.39		0 - 1.82
Azelaic	17	0.28		0 - 13.4
3-methyladipic	12	12.01	↑	0 - 2.58
Ethylmalonic	2, 12	5.16		0 - 18.49
Methylsuccinic	12	0.18		0 - 3.15
3-hydroxysebacic		13.79		0 - 37.66
2-Hydroxybutyric	5, 12, 13	2.01	↑	0 - 1.54
2-hydroxyhexanoic				0 - 1.8
3-hydroxyhexanoic				0 - 4.74
5-hydroxyhexanoic		n.d.		0 - 4.48
7-hydroxyoctanoic				-
2-hydroxyadipic				0 - 17.68
3-hydroxyadipic				0 - 1.27
3-hydroxydodecanoic				-
3-oxoadipic				-
3-oxosebacic				-
2-hexenedioic				-
Decenedioic				-
Decadienedioic				-
2-hydroxysebacic				-
Hexanoylglycine				-
Butyrylglycine				-

5. Промежуточные продукты гликолиза и метаболизма углеводов				
Глюкоза		N		N (норма)
Проба на редуцирующие вещества		сл.	↑	отрицательная
Lactic	1, 8, 12, 13	41.13		6.32 - 142.49
Pyruvic	1, 12, 14	present		-
2-Hydroxybutyric	4, 12, 13	2.01	↑	0 - 1.54
2,3-Dihydroxybutiric		51.06		0 - 122.74
2,4-Dihydroxybutiric		5.88		0 - 24.4
3,4- Dihydroxybutiric		77.27		0 - 82.8
Rythronic				0 - 22
Uracil	2, 6	6.29		0 - 10.87
Pantoyllactone				-
Threonolactone				-
Erythrono-1,4-tetronic				0 - 1.49

6. Метаболиты пиримидинов				
Uracil	2, 5	6.29		0 - 10.87
Thymine		n.d.		n.d.
Orotic	12, 13, 14	n.d.		n.d.

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ФИО Врача	доц. Гречанина Ю.Б.	Пол	м	Дата приема	08.04.2013

Вещество	Состоит в группе(ах)	Результат		Норма	
7. Метаболиты грибков и дрожжей					
Проба на индикан		-		отрицательная	-
Sumiki's (5-hydroxymethyl-2-furoic)		2.36		0 - 55.12	Umol/mmol KREA
2,5 furandicarboxylic		n.d.		0 - 23.4	Umol/mmol KREA
Furoylglicine	17	n.d.		n.d.	Umol/mmol KREA
Tartaric	1, 9, 17	n.d.		n.d.	mmol/mol KREA
Methylmaleic	1	1.76		0 - 1.92	Umol/mmol KREA
Oxoglutaric	1, 9, 11, 12, 13, 14	182.72		0 - 677.2	Umol/mmol KREA
Fumaric	1, 11, 12	6.02		1.2 - 25.25	mmol/mol KREA
Malic	1, 12	n.d.		0 - 47.26	mmol/mol KREA
3-hydroxymethylglutaric	1, 11, 12	14.18		0 - 33.1	Umol/mmol KREA
8. Метаболиты бактерий					
3-(3-Hydroxyphenyl)-3-hydroxypropionic acid (Clostridial marker) (Phe, Tyr)		42	↑	0 - 18.14	Umol/mmol KREA
3-hydroxyphenylpropanoic (Phe, Tyr)				n.d.	Umol/mmol KREA
Hydrocaffeic (DHPPA) (beneficial bacteria)				-	Umol/mmol KREA
3-Hydroxyphenylacetic (Phe, Tyr)		22.2	↑	0 - 12.4	Umol/mmol KREA
3-hydroxyhippuric (Phe, Tyr)	11	5.15	↑	n.d.	Umol/mmol KREA
p-hydroxyhippuric (Phe, Tyr)	11, 16	427.3	↑	0 - 405.21	Umol/mmol KREA
4-hydroxybenzoic (Phe, Tyr)	11	137.65		15.92 - 273.2	Umol/mmol KREA
p-hydroxyphenylacetic (Phe, Tyr)	11	331.49		0 - 837.9	Umol/mmol KREA
2-hydroxyphenylacetic (Phe, Tyr)	11, 13	1.07		0 - 11	Umol/mmol KREA
Hippuric (Phe, Tyr)	9, 11, 15, 16	5092.18	↑	0 - 2181.85	Umol/mmol KREA
Benzoic (Phe, Tyr)	15	n.d.		0 - 2.14	mmol/mol KREA
p-Cresol (Phe, Tyr)	14	1403.15	↑	0 - 281.05	Umol/mmol KREA
4 hydroxycyclohexylcarboxylic (Phe, Tyr)	11	n.d.		0 - 2.02	Umol/mmol KREA
4-hydroxycyclohexylacetic (Phe, Tyr)	11			n.d.	Umol/mmol KREA
Indoleacetic (Trp)	11	108.38		0 - 261.14	Umol/mmol KREA
Gentisic (Trp)		45.06		0 - 199.1	Umol/mmol KREA
Indolelactic (Trp)	11			-	Umol/mmol KREA
5-Hydroxyindoleacetic (Trp)	10, 11	576.23		0 - 583.56	Umol/mmol KREA
Lactic	1, 5, 12, 13	41.13		6.32 - 142.49	mmol/mol KREA
Glycolic	3, 12	52.91		10.79 - 607.58	mmol/mol KREA
Glyceric	3, 12	n.d.		n.d.	mmol/mol KREA
Salicyluric	14	26.44	↑	n.d.	Umol/mmol KREA
Tricarballylic				-	Umol/mmol KREA
Methylcitric	12, 15			-	Umol/mmol KREA
3-hydroxypropionic	2, 12, 13, 15	13.32		0 - 24.66	Umol/mmol KREA
5-Oxoproline	2, 9, 13, 14, 15	116.5	↑	15.82 - 74.46	mmol/mol KREA
Levulinic		16.05		0 - 21.69	Umol/mmol KREA
9. Метаболиты костной и соединительной ткани, нарушении обмена АК Пролина (Pro), Глицина (Gly)					
Phosphoric (Витамин D)		322.1		0 - 871.43	Umol/mmol KREA
Hydroxyproline dipeptid (Витамин C)	12	165.95	↑	n.d.	Umol/mmol KREA
5-Oxoproline	2, 8, 13, 14, 15	116.5	↑	15.82 - 74.46	mmol/mol KREA
Tartaric (Гиалуроновая кислота)	1, 7, 17	n.d.		n.d.	mmol/mol KREA
Oxoglutaric (His, Arg, Pro)	1, 7, 11, 12, 13, 14	182.72		0 - 677.2	Umol/mmol KREA
↓ или ↑↑ Hippuric (Gly)	8, 11, 15, 16	5092.18	↑	0 - 2181.85	Umol/mmol KREA

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ФИО Пациента	[redacted]А.		Возраст	11м	Регистрационный №	543
ФИО Врача	доц. Гречанина Ю.Б.		Пол	м	Дата приема	08.04.2013

Вещество	Состоит в группе(ах)	Результат		Норма	
10. Метаболиты нейротрансмиттеров					
Vanilmandelic (Норадреналин)	2, 12, 13	1031	↑	0 - 778.6	Umol/mmol KREA
Homovanilic (Допамин)	2, 12, 13	119.03		0 - 365.66	Umol/mmol KREA
5-Hydroxyindoleacetic (Серотонин)	8, 11	576.23		0 - 583.56	Umol/mmol KREA
3,4-dihydroxyphenylacetic (Допамин)		38.93		0 - 49	Umol/mmol KREA
p-hydroxymandelic (тирамин, p-октапамин, p-синефрин)		165.53		0 - 173.49	Umol/mmol KREA
11.1 Метаболиты АК Фенилаланина (Phe), Тирозина (Tyr)					
2-hydroxyphenylacetic (**Phe**, Tyr)	8, 13	1.07		0 - 11	Umol/mmol KREA
p-hydroxyphenylacetic (**Phe**, Tyr)	8	331.49		0 - 837.9	Umol/mmol KREA
Phenylactic (**Phe**, Tyr)	14			-	Umol/mmol KREA
Mandelic (**Phe**, Tyr)	14			-	Umol/mmol KREA
Phenylpiruvic (**Phe**, Tyr)				-	Umol/mmol KREA
Phenyllactic (**Phe**, Tyr)				-	Umol/mmol KREA
↓ Sumiki's (5-hydroxymethyl-2-furoic) (Phe)		2.36		0 - 55.12	Umol/mmol KREA
N-acetyltirosine (Tyr)	15	0.06	↑	n.d.	mmol/mol KREA
4-hydroxyphenylpyruvic (Phe, **Tyr**)	12, 13, 15	9.52		0 - 28.57	Umol/mmol KREA
Hydroxyphenyllactic (Phe, **Tyr**)	12, 13, 15	47.66		0 - 167.01	Umol/mmol KREA
Homogentisic (Phe, **Tyr**)	12, 13			-	Umol/mmol KREA
4-hydroxybenzoic (Phe, Tyr)	8	137.65		15.92 - 273.2	Umol/mmol KREA
p-hydroxyhippuric (Phe, Tyr)	8, 16	427.3	↑	0 - 405.21	Umol/mmol KREA
3-hydroxyhippuric (Phe, Tyr)	8	5.15	↑	n.d.	Umol/mmol KREA
Hippuric (Phe, Tyr)	8, 9, 16, 16	5092.18	↑	0 - 2181.85	Umol/mmol KREA
4-hydroxycyclohexylcarboxylic (Phe, Tyr)	8	n.d.		0 - 2.02	Umol/mmol KREA
4-hydroxycyclohexylacetic (Phe, Tyr)	8			n.d.	Umol/mmol KREA
Fumaric (Phe, Tyr)	1, 7, 12	6.02		1.2 - 25.25	mmol/mol KREA
11.2 Метаболиты АК Триптофана (Trp), Лизина (Lis), Гистидина (His), Аргинина (Arg)					
Pimelic (Lys)	4	0.39		0 - 1.82	mmol/mol KREA
Glutaric (Lys, Trp, B2)	**12, 14**	**1.51**		**0 - 3.38**	mmol/mol KREA
5-Hydroxyindoleacetic (Trp)	8, 10	576.23		0 - 583.56	Umol/mmol KREA
Indoleacetic (Trp)	8	108.38		0 - 261.14	Umol/mmol KREA
Indolelactic (Trp)	8			-	Umol/mmol KREA
Oxoglutaric (His, Arg, Pro)	1, 7, 9, 11, 12, 13, 14	182.72		0 - 677.2	Umol/mmol KREA
11.3 Кетоз; метаболиты АК с разветвленной цепью: Лейцина (Leu), Изолейцина (Ile), Валина (Val)					
Тест на кетокислоты при лейцинозе		отр.		отрицательный	-
3-methylglutaric (Leu)		0.16		0 - 0.5	Umol/mmol KREA
3-Methylglutaconic (Leu)		38.07	↑	0 - 36.41	Umol/mmol KREA
Isovalerilglicine (Leu)				n.d.	Umol/mmol KREA
3-methylcrotonylglycine (Leu)				-	Umol/mmol KREA
2-Hydroxyisovaleric (Leu)				0 - 15.04	Umol/mmol KREA
3-hydroxyisovaleric (Leu)	12	18.65	↑	0 - 13.11	Umol/mmol KREA
3-hydroxymethylglutaric (Leu)	1, 7, 12	14.18		0 - 33.1	Umol/mmol KREA
Hydroxyisobutyric (Ile)		9.85		0 - 14.48	Umol/mmol KREA
Erythronilic (Ile)		116.27	↑	0 - 110.63	Umol/mmol KREA
2-Ethylhydracrylic (Ile)		33.64	↑	0 - 1.2	Umol/mmol KREA
Tyglylglycine (Ile)	1, 2	21.93	↑	n.d.	Umol/mmol KREA
2-Methylbutyrylglycine (Ile)				-	Umol/mmol KREA
3-Hydroxyisobutyric (Val, тимин)		22.49	↑	0 - 16.6	Umol/mmol KREA
Isobutyrylglycine (Val)				n.d.	Umol/mmol KREA
Succinic (Leu, Ile, Val)	1, 2, 12, 13	2.78		2.51 - 127.6	mmol/mol KREA

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ФИО Врача	доц. Гречанина Ю.Б.	Пол	м	Дата приема	08.04.2013

Вещество	Состоит в группе(ах)	Результат		Норма	
11.4 Метаболиты АК Глутамина (Gln), Глутаминовой кислоты (Glu), Аспарагиновой кислоты (Asp), истощения глутатиона					
↓5-Oxoproline (↓glutatione)	14	116.5	↑	15.82 - 74.46	mmol/mol KREA
↓Citric (↓glutatione)	1	31.53		25.7 - 648.57	mmol/mol KREA
*Aconitic (↓glutatione)	1, 2, 13, 14	10.47		0 - 35.51	Umol/mmol KREA
Oxoglutaric (Glu, Gln)	1, 7, 9, 11, 12, 13, 14	182.72		0 - 677.2	Umol/mmol KREA
N-Acetyl-L-aspartic (Asp, Glu, Gln, Cu)	13	464.75	↑↑	0 - 32.3	mmol/mol KREA
12.1 Индикаторы активности витаминов B1 (тиамина), B3 (никотинамида, PP)					
2-ketoisovaleric (B1, B3)	12, 13			-	mmol/mol KREA
Lactic (B1, B3)	1, 5, 8, 12, 13	41.13		6.32 - 142.49	Umol/mmol KREA
Pyruvic (B1, B3)	1, 5, 12, 14	present		-	Umol/mmol KREA
2-Hydroxybutyric (B1, B3)	4, 5, 12, 13	2.01	↑	0 - 1.54	mmol/mol KREA
Oxoglutaric (B1, B3)	1, 7, 9, 11, 12, 13, 14	182.72		0 - 677.2	Umol/mmol KREA
Fumaric (B3)	1, 7, 11	6.02		1.2 - 25.25	mmol/mol KREA
Malic (B3)	1, 7	n.d.		0 - 47.26	mmol/mol KREA
Isocitric (B3)	1, 13	56.8		5.7 - 133.99	mmol/mol KREA
↓Homovanilic (B3)	2, 10, 12, 13	119.03		0 - 365.66	Umol/mmol KREA
Orotic (B3)	6, 12, 13, 14	n.d.		n.d.	mmol/mol KREA
12.2 Индикаторы активности витаминов B2 (рибофлавина), B5 (пантотеновой кислоты)					
Glutaric (B2)	11, 12, 14	1.51		0 - 3.38	mmol/mol KREA
Ethylmalonic (B2, B5)	2, 4	5.16		0 - 18.49	Umol/mmol KREA
Methylsuccinic (B2, B5)	4	0.18		0 - 3.15	Umol/mmol KREA
3-methyladipic (B2, B5)	4	12.01	↑	0 - 2.58	mmol/mol KREA
Adipic (B2, B5)	4	7.98		0 - 36.92	mmol/mol KREA
Suberic (B2, B5)	4	0.2		0 - 9.6	mmol/mol KREA
Oxoglutaric (B2, B5)	1, 7, 9, 11, 12, 13, 14	182.72		0 - 677.2	Umol/mmol KREA
↓Vanilmandelic (B2)	2, 10, 12, 13	1031	↑	0 - 778.6	Umol/mmol KREA
↓Homovanilic (B2)	2, 10, 12, 13	119.03		0 - 365.66	Umol/mmol KREA
2-ketoisovaleric (B1, B3)	12, 13			-	Umol/mmol KREA
12.3 Индикаторы активности витамина B6 (пиридоксина)					
Orotic	6, 12, 13, 14	n.d.		n.d.	mmol/mol KREA
Oxalic	3	41.67		30.05 - 219.8	mmol/mol KREA
Glycolic	3, 8	52.91		10.79 - 607.58	mmol/mol KREA
Glyceric	3, 8	n.d.		n.d.	mmol/mol KREA
↓Vanilmandelic	2, 10, 12, 13	1031	↑	0 - 778.6	Umol/mmol KREA
↓Homovanilic	2, 10, 12, 13	119.03		0 - 365.66	Umol/mmol KREA
12.4 Индикатор активности витамина B8 (биотина, H)					
3-Hydroxyisovaleric	11	18.65	↑	0 - 13.11	Umol/mmol KREA
Methylcitric	8, 15			-	Umol/mmol KREA
3-hydroxypropionic	2, 8, 13, 15	13.32		0 - 24.66	Umol/mmol KREA
Lactic	1, 5, 8, 12, 13	41.13		6.32 - 142.49	mmol/mol KREA
12.5 Индикаторы активности коэнзима Q10					
3-hydroxymethylglutaric	1, 7, 11	14.18		0 - 33.1	Umol/mmol KREA
Lactic	1, 5, 8, 12, 13	41.13		6.32 - 142.49	mmol/mol KREA
Pyruvic	1, 5, 12, 14	present		-	Umol/mmol KREA
Succinic	1, 2, 11, 13	2.78		2.51 - 127.6	mmol/mol KREA
Glutaric	11, 12, 14	1.51		0 - 3.38	mmol/mol KREA
2-Hydroxybutyric	4, 5, 12, 13	2.01	↑	0 - 1.54	mmol/mol KREA

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ФИО Пациента	[redacted]А.	Возраст	11м	Регистрационный №	543
ФИО Врача	доц. Гречанина Ю.Б.	Пол	м	Дата приема	08.04.2013

Вещество	Состоит в группе(ах)	Результат		Норма	
12.6 Индикатор активности витамина С (аскорбиновой кислоты)					
Hydroxyproline dipeptid	9	165.95	↑	n.d.	Umol/mmol KREA
Hydroxyphenyllactic	11, 13	47.66		0 - 167.01	Umol/mmol KREA
4-hydroxyphenylpyruvic	11, 13, 15	9.52		0 - 28.57	Umol/mmol KREA
Homogentisic	11, 13			-	Umol/mmol KREA
13.1 Индикаторы недостаточности микроэлементов: Железа (Fe), Меди (Cu)					
Hydroxyphenyllactic (Fe)	11, 12	47.66		0 - 167.01	Umol/mmol KREA
4-hydroxyphenylpyruvic (Fe, Cu)	11, 12, 15	9.52		0 - 28.57	Umol/mmol KREA
Homogentisic (Fe)	11, 12			-	Umol/mmol KREA
↓Vanilmandelic (Fe, Cu)	2, 10, 12	1031	↑	0 - 778.6	Umol/mmol KREA
↓Homovanilic (Fe)	2, 10, 12, 13	119.03		0 - 365.66	Umol/mmol KREA
2-hydroxyphenylacetic (Fe)	8, 11	1.07		0 - 11	Umol/mmol KREA
Aconitic (Fe)	1, 2, 11, 14	10.47		0 - 35.51	Umol/mmol KREA
N- Acetyl-L-aspartic (Cu, Asp, Glu, Gln)	11	464.75	↑↑	0 - 32.3	mmol/mol KREA
13.2 Индикаторы недостаточности микроэлемента: Магния (Mg)					
Succinic	1, 2, 11, 12	2.78		2.51 - 127.6	mmol/mol KREA
Oxoglutaric	1, 7, 9, 11, 12, 14	182.72		0 - 677.2	Umol/mmol KREA
Isocitric	1, 12, 13, 14	56.8		5.7 - 133.99	mmol/mol KREA
3-hydroxypropionic	2, 8, 12, 15	13.32		0 - 24.66	Umol/mmol KREA
5-Oxoproline	2, 8, 9, 14	116.5	↑	15.82 - 74.46	mmol/mol KREA
↓Homovanilic	2, 10, 12, 13	119.03		0 - 365.66	Umol/mmol KREA
2-ketoisovaleric	12			-	Umol/mmol KREA
Orotic	6, 12, 14	n.d.		n.d.	mmol/mol KREA
13.3 Индикаторы недостаточности других микроэлементов:					
Марганеца (Mn), Цинка (Zn), Хрома (Cr), Ванадия (V), Селена (Se)					
Isocitric (Mn)	1, 12, 13, 14	56.8		5.7 - 133.99	mmol/mol KREA
Lactic (Zn)	1, 5, 8, 12	41.13		6.32 - 142.49	mmol/mol KREA
2-Hydroxybutyric (Cr, V)	4, 5, 12	2.01	↑	0 - 1.54	mmol/mol KREA
5-Oxoproline (Se)	8, 9, 14, 15	116.5	↑	15.82 - 74.46	mmol/mol KREA
14. Метаболиты, которые могут быть повышены при отравлении					
↓ *или* ↑ *5-Oxoproline*	8, 9, 13, 11, 15	116.5	↑	15.82 - 74.46	mmol/mol KREA
Orotic	6, 12, 13	n.d.		n.d.	mmol/mol KREA
Glutaric	11, 12	1.51		0 - 3.38	mmol/mol KREA
Oxoglutaric (изменяется при гипераммонемии, отравлении As, Hg, Cd)	1, 7, 9, 11, 12, 13	182.72		0 - 677.2	Umol/mmol KREA
Pyruvic (отравление As, Pb, Hg, Cd)	1, 5, 12	present		-	Umol/mmol KREA
Citric (отравление Al, Hg, As)	1, 11	31.53		25.7 - 648.57	mmol/mol KREA
Aconitic (отравление Al, Hg, As)	1, 2, 11, 13	10.47		0 - 35.51	mmol/mol KREA
Isocitric (отравление Al)	1, 12, 13	56.8		5.7 - 133.99	Umol/mmol KREA
Phenol (компонент пластмасс, содержится в выхлопных газах)		13.05		0 - 20.42	Umol/mmol KREA
p-Cresol (отравление фенолом)	8	1403.15	↑	0 - 281.05	Umol/mmol KREA
Mandelic (отравление толуолом, ароматическими растворителями)	11			-	Umol/mmol KREA
Phenoxyacetic (отравление пестицидами; прием пенициллина V)		n.d.		0 - 141.61	Umol/mmol KREA
Salicyluric (отравление аспирином, прием аспартама)	8	26.44	↑	n.d.	Umol/mmol KREA
Phenobarbital				-	Umol/mmol KREA

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ФИО Врача	доц. Гречанина Ю.Б.	Пол	м	Дата приема	08.04.2013

Вещество	Состоит в группе(ах)	Результат		Норма	
15.1 Метаболиты, которые могут повышаться при приеме противосудорожных препаратов					
(могут вызывать кетоз; изменения в группах метаболитов– 4, 11.3)					
N-Acetyltirosine	11	0.06	↑	n.d.	mmol/mol KREA
4-hydroxyphenylpyruvic	11, 12, 13	9.52		0 - 28.57	Umol/mmol KREA
Methylcitric	8, 12			-	Umol/mmol KREA
Valproic				-	Umol/mmol KREA
2-n-propyl-3-hydroxyvaleric				-	Umol/mmol KREA
(Z)-2-propyl-3-oxopentanoic				-	Umol/mmol KREA
Hexane-1,3-dicarboxylic (2-n-propylglutaric)				-	Umol/mmol KREA
3-Hydroxypropionic	2, 8, 12, 13	13.32		0 - 24.66	Umol/mmol KREA
4-hydroxybutyric (Метаболит ГАМК)	17			-	Umol/mmol KREA
15.2 Другие лекарственные препараты и метаболиты лекарственных препаратов					
Glycerol	17	n.d.		0 - 1184	mmol/mol KREA
Maleic		n.d.		n.d.	Umol/mmol KREA
3-hydroxybenzoic				n.d.	Umol/mmol KREA
Cyclohexanone				-	Umol/mmol KREA
Methylparaben				-	Umol/mmol KREA
Acetylsalicylate				-	Umol/mmol KREA
Paracetamol		280.24		-	Umol/mmol KREA
Paracetamol glucopyranoside		present		-	Umol/mmol KREA
Benzamid				-	Umol/mmol KREA
2-aminobenzoic				-	Umol/mmol KREA
Pantothenic		2.35		0 - 15.62	Umol/mmol KREA
Ascorbic				-	Umol/mmol KREA
Chloramphenicol				-	Umol/mmol KREA
5-Oxoproline , (прием противовирусных или противомикробных препаратов; ацетоминофена, vigabatrin, nutramigen)	2, 8, 9, 13, 14	116.5	↑	15.82 - 74.46	mmol/mol KREA
Benzoic (прием бензоатов)	8	n.d.		0 - 2.14	mmol/mol KREA
Hippuric (прием бензоатов)	8, 9, 11, 16	5092.18	↑	0 - 2181.85	Umol/mmol KREA
16. Метаболиты приема полифенолов и флавонидов с пищей					
Ferulic				0 - 17.76	Umol/mmol KREA
Hippuric	8, 9, 11, 15	5092.18	↑	0 - 2181.85	Umol/mmol KREA
Hydroxycinnamic				-	Umol/mmol KREA
Caffeic				-	Umol/mmol KREA
p-hydroxyhippuric	8, 11	427.3	↑	0 - 405.21	Umol/mmol KREA
3-methoxy-4-hydroxyphenyl-3-hydroxypropionic		14.74		0 - 37.37	Umol/mmol KREA
4-hydroxyphenylhydroxylacrylate				-	Umol/mmol KREA
m-Coumaric				-	Umol/mmol KREA
Sinapic				-	Umol/mmol KREA
Galic				-	Umol/mmol KREA
Pyrogallol				-	Umol/mmol KREA
Guaicol				-	Umol/mmol KREA
Pyrocatechol				-	Umol/mmol KREA
Hydroquinone				-	Umol/mmol KREA

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ФИО Пациента	[redacted]		Возраст	11м	Регистрационный №	543
ФИО Врача	доц. Гречанина Ю.Б.		Пол	м	Дата приема	08.04.2013

Вещество	Состоит в группе(ах)	Результат		Норма	
17. Прочие метаболиты и вещества					
Тест на сульфиды (консерванты Е221 – Е223)	2	100	↑	отрицательный	мг/л
Urea		11.45		0 - 1979.48	Umol/mmol KREA
Uric				0 - 20.59	Umol/mmol KREA
Tartaric (Винная кислота)	1, 7, 9	n.d.		n.d.	mmol/mol KREA
Furoylglicine (образуется в жареной пище)	7	n.d.		n.d.	Umol/mmol KREA
Glycerol	15	n.d.		0 - 1184	mmol/mol KREA
Vanillic		83.04	↑	n.d.	Umol/mmol KREA
3,5-dihidroxybenzoic				n.d.	Umol/mmol KREA
Isocitric lactone		n.d.		0 - 69.79	Umol/mmol KREA
Citric acid ethyl ester				-	Umol/mmol KREA
Caffeine				-	Umol/mmol KREA
4-hydroxybutyric	15			-	Umol/mmol KREA
Pimelic (метаболит пластмас)	4, 11	0.39		0 - 1.82	mmol/mol KREA
Azelaic (метаболит пластмас)	4	0.28		0 - 13.4	mmol/mol KREA
2-methylglutaric				-	Umol/mmol KREA
2-methylglutaconic				-	Umol/mmol KREA
5hydroxy-n-valeric		n.d.		0 - 1.68	Umol/mmol KREA
Caproic		1.77		0 - 40.54	Umol/mmol KREA
Caprilic		3.54		0 - 97.67	Umol/mmol KREA
Pelargonic		7.81		0 - 266.41	Umol/mmol KREA
Capric				-	Umol/mmol KREA
Lauric		107.73	↑	0 - 63.25	Umol/mmol KREA
Miristic				-	Umol/mmol KREA
Linoleic		5		0 - 67.08	Umol/mmol KREA
Oleic		22.83		0 - 312.33	Umol/mmol KREA
Stearic		56.66		74.1 - 1443.05	Umol/mmol KREA
Arahidonic				-	Umol/mmol KREA
Glucosan				-	Umol/mmol KREA
Vanyllactic				-	Umol/mmol KREA

КОММЕНТАРИИ:

Выявлено значительное повыние N-ацетил-L-аспарагиновой кислоты

Выявлены изменения метаболитов:

- серы;
- соединительной ткани;
- кетоза, АК с разветвленной цепью;
- недостаточности С, Cu;
- чрезмерного роста бактерий в ЖКТ;

- Точность анализа снижена в связи с высоким уровнем креатинина

16 мая 2013 г. Подпись Канюка М.В.

There are the following disorders of AA metabolism

- **Breakdown of protein lead to the formation of a great amount of nitrogen – a substance, which is highly toxic for CNS. Nitrogen is usually converted in urea and released with urine.**
- ***Defects of enzymes of urea cycle and other disorders of detoxification of ammonia are manifested clinically in the form of encephalopathy and hyperammonemia**

***Study of metabolism should include analysis of amino acids of blood and urine in determination of orotic acid in urine.**

Disorder of transport of amino acids

Defects of intestine and/or renal transport of AA can be:

- asymptomatic
- Manifested clinically as a deficiency of essential amino acids or as a result of the disorder of AA transport (e.g. tryptophan in Hartnup disease)
- Followed by the increase of uric concentration of unsolved AA (e.g. cystine in cystinuria)

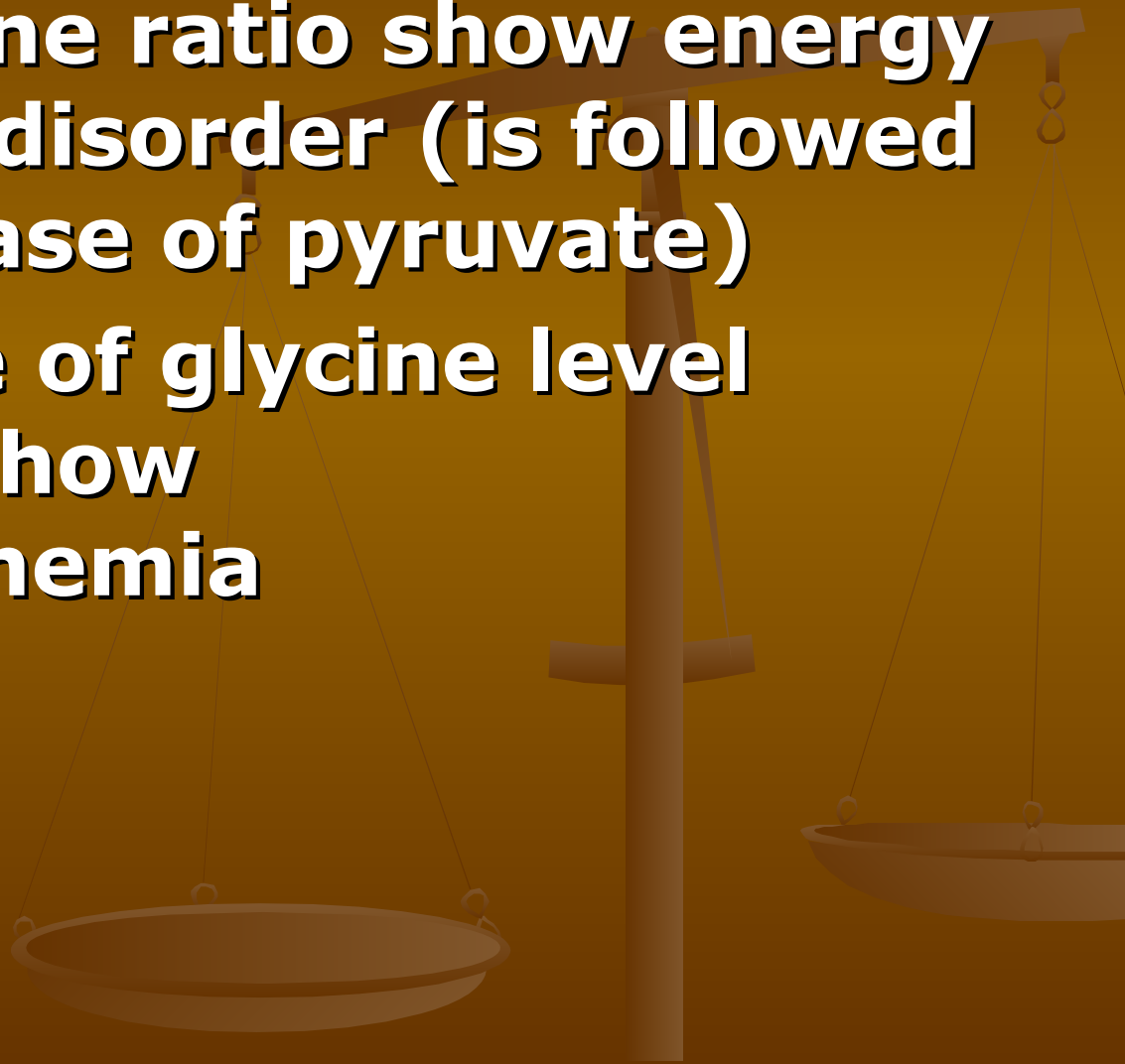
In the result of accumulation of toxic metabolites in inborn errors of AA metabolism

- Pathologic changes of different organs and systems are developed;
- The risk of the development of encephalopathy increases;
- Stable neurological disorders appear

Clinical features of some aminoacidopathies

- Combination of mental retardation (MR) with convulsions (non ketotic hyperglycinemia, PKU, disorder of metabolism of AA of urea cycle, hyperlysinemia);
- Combination of MR with pathology of vision (homocystinuria);
- Combination of MR with skin affection (PKU, inherent xanturenuria, histidinemia);
- Combination of the affection of the liver and CNS (argininemia);
- Hearing disorder (hyperprolinemia).

- Alanine/lysine ratio show energy metabolism disorder (is followed by the increase of pyruvate)
- The increase of glycine level (+alanine) show hyperammonemia



Methods, which are used for diagnosis of disorders of AA metabolism

- Urinolysis – the qualitative and quantitative reactions. Material for study – morning urine
- Thin-layer chromatography. Material – blood, daily urine.
- Classical biochemical values and enzymes (glucose, Ca, P, LDH, Cl and other)
- Quantitative analysis of AA by HELC method, Waters.
- Mass screening – newborn programs: diagnosis of PKU. Material dry blood spots
- Perspective studies – the qualitative analysis of organic and fatty acids using tandem mass-spectrometry

The content of amino acids in biological liquids depends on metabolic condition:

- If sampling is performed after feeding, the content of essential amino acids increases (LYS, PHE, TYR, VAL, LEU, ILE, GLN, CIT);
- Long-term fasting with ketosis – the increase of amino acids with branching chain (VAL, ILE, LEU)

Unspecific changes:

- hemolysis, late centrifugation cause:

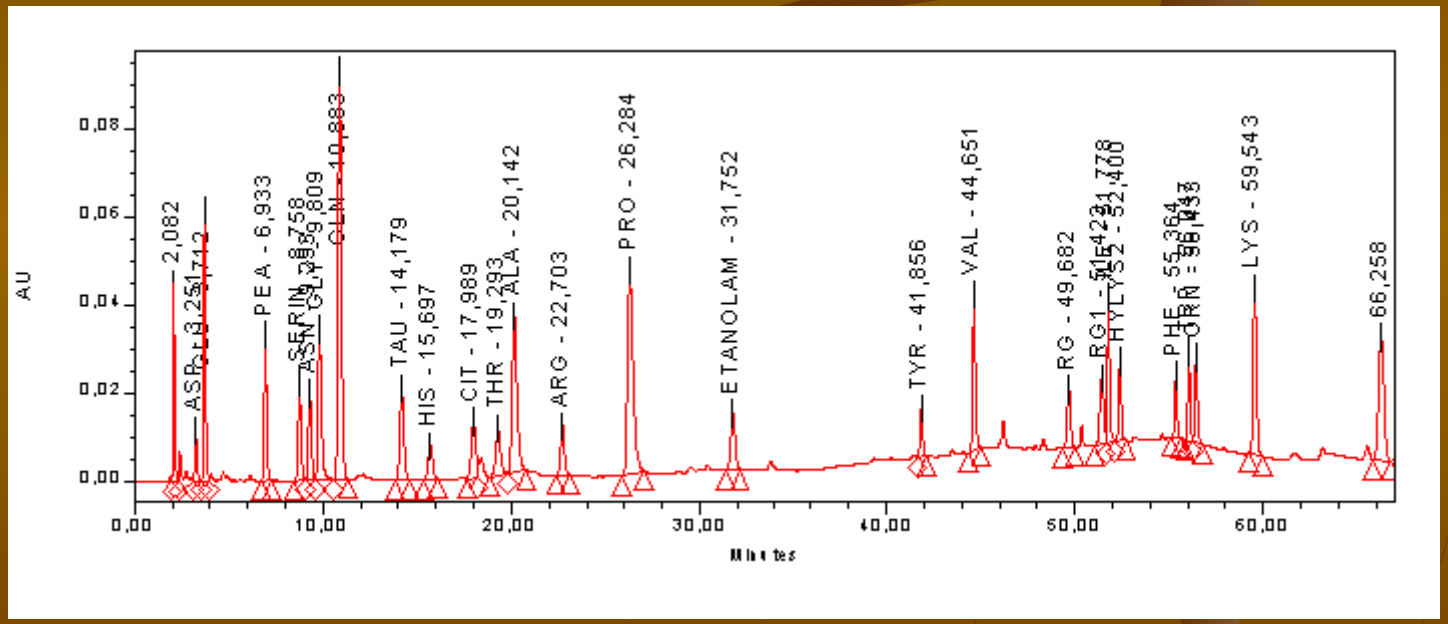
↓ARG, ↑ASP, GLU, ORN, TAU;

- Long-term preservation of samples at room temperature - ↓ GLN, ASN, CYS, HOCYS; ↑ASP, GLU

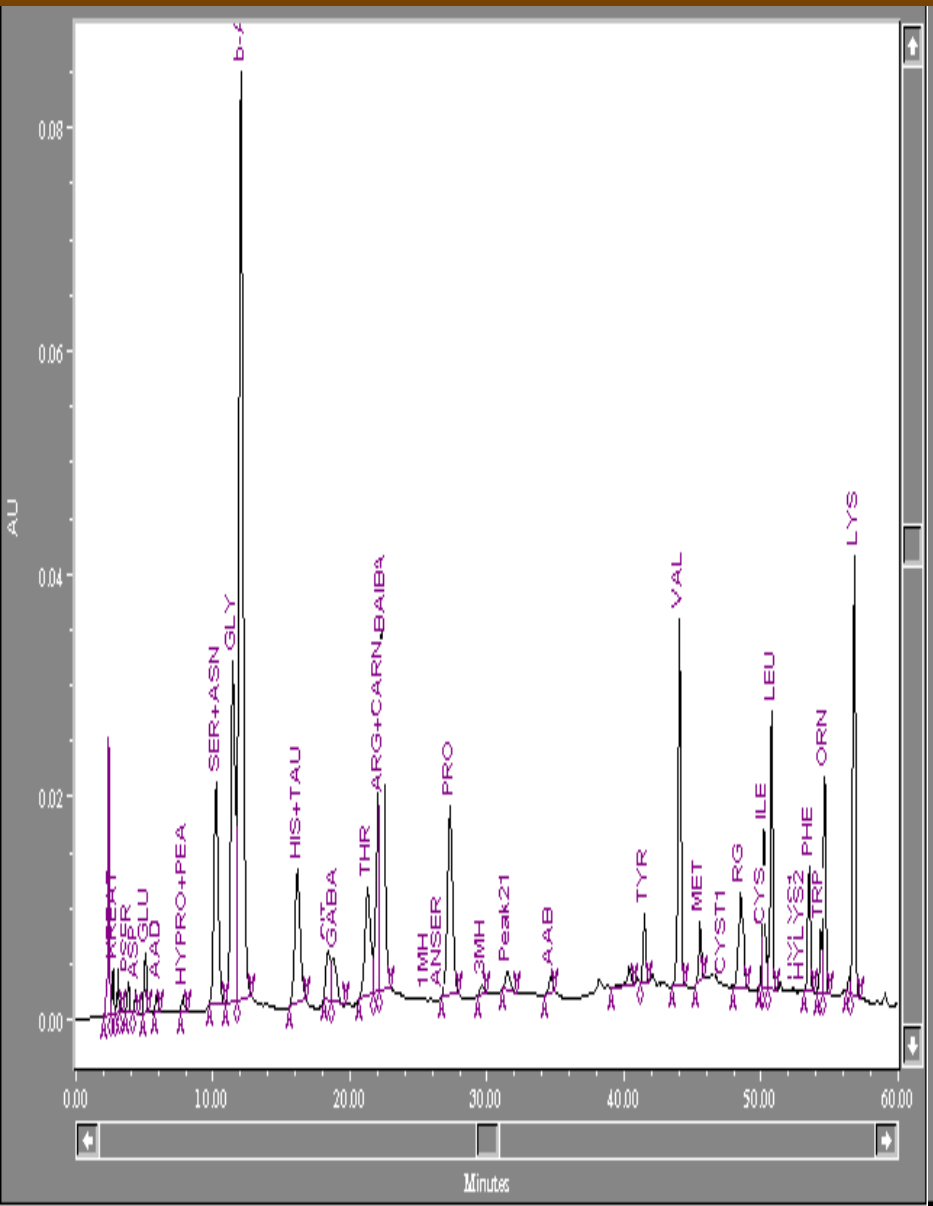
Profile of amino acids

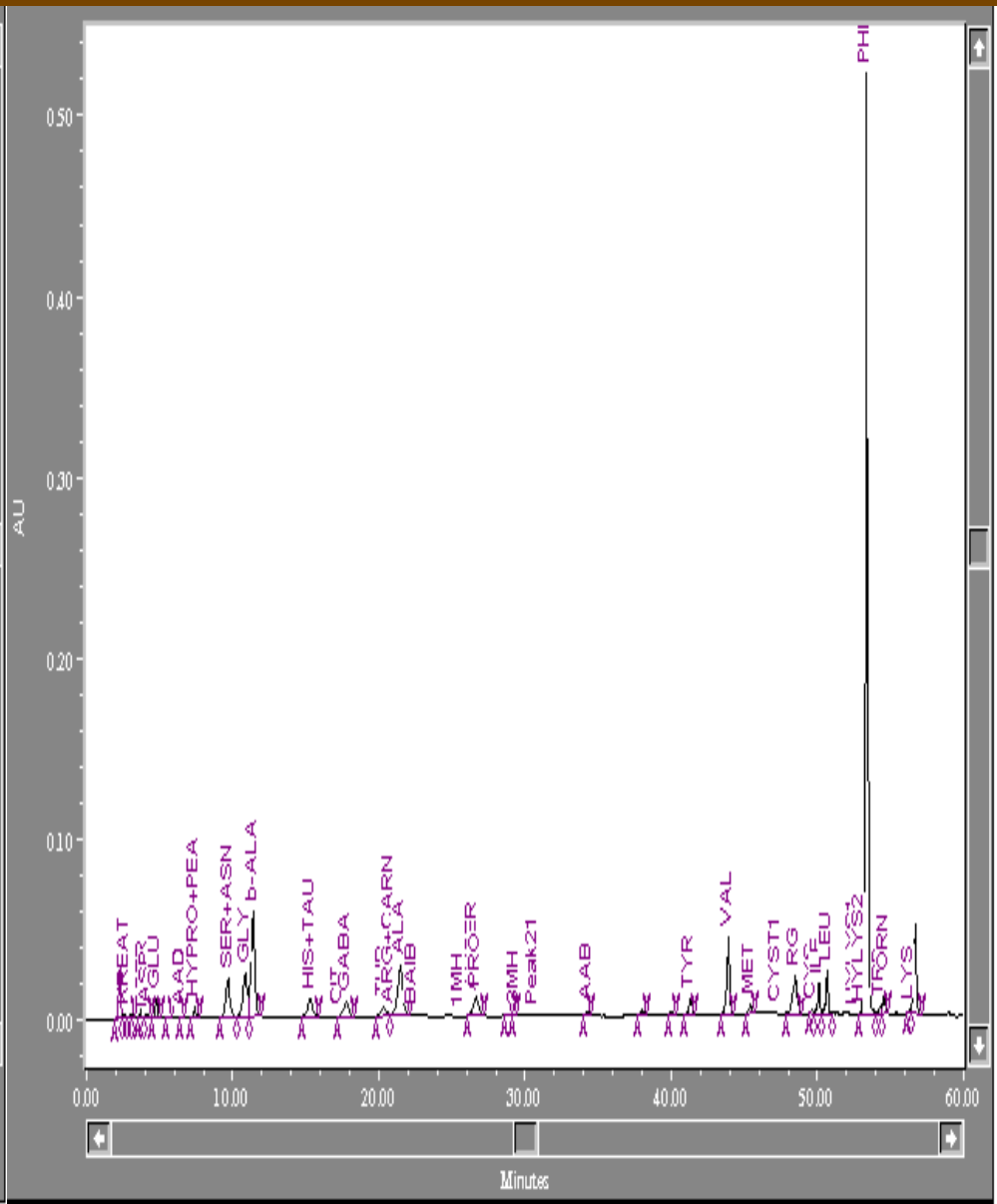
- Alimentary upload
- Liver disease
- Use (medicines,diet and other) medium-chain triglycerides
- Use of EDTA as a coagulant in sampling
- Treatment with benzoate, pyropyruvic and valproic acids
- Carnitine defect

Chromatographic profile. Prolinemia

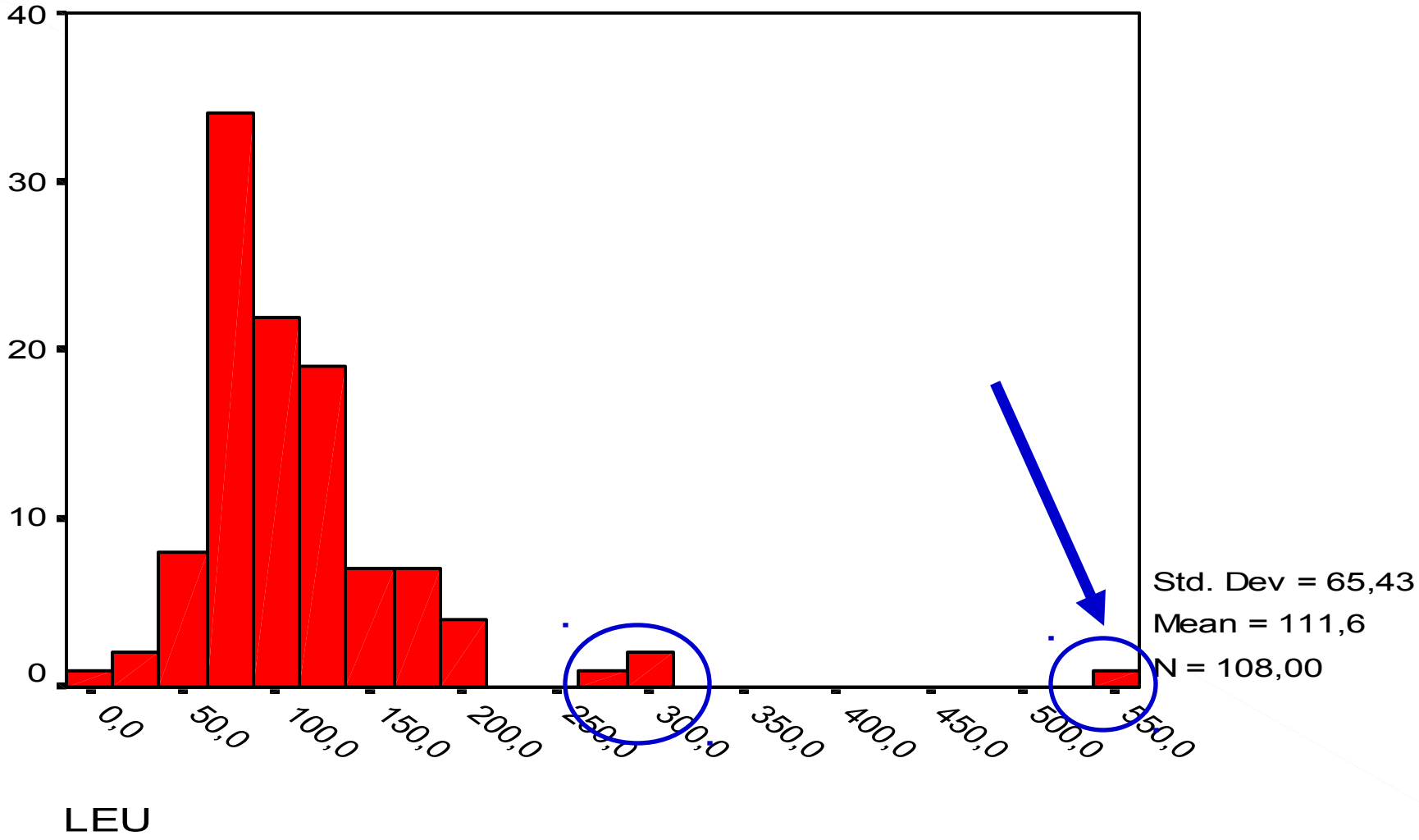


Chromatographs of blood serum are within norm in PKU





Laboratory criteria of establishment of the diagnosis of concrete aminoacidopathy

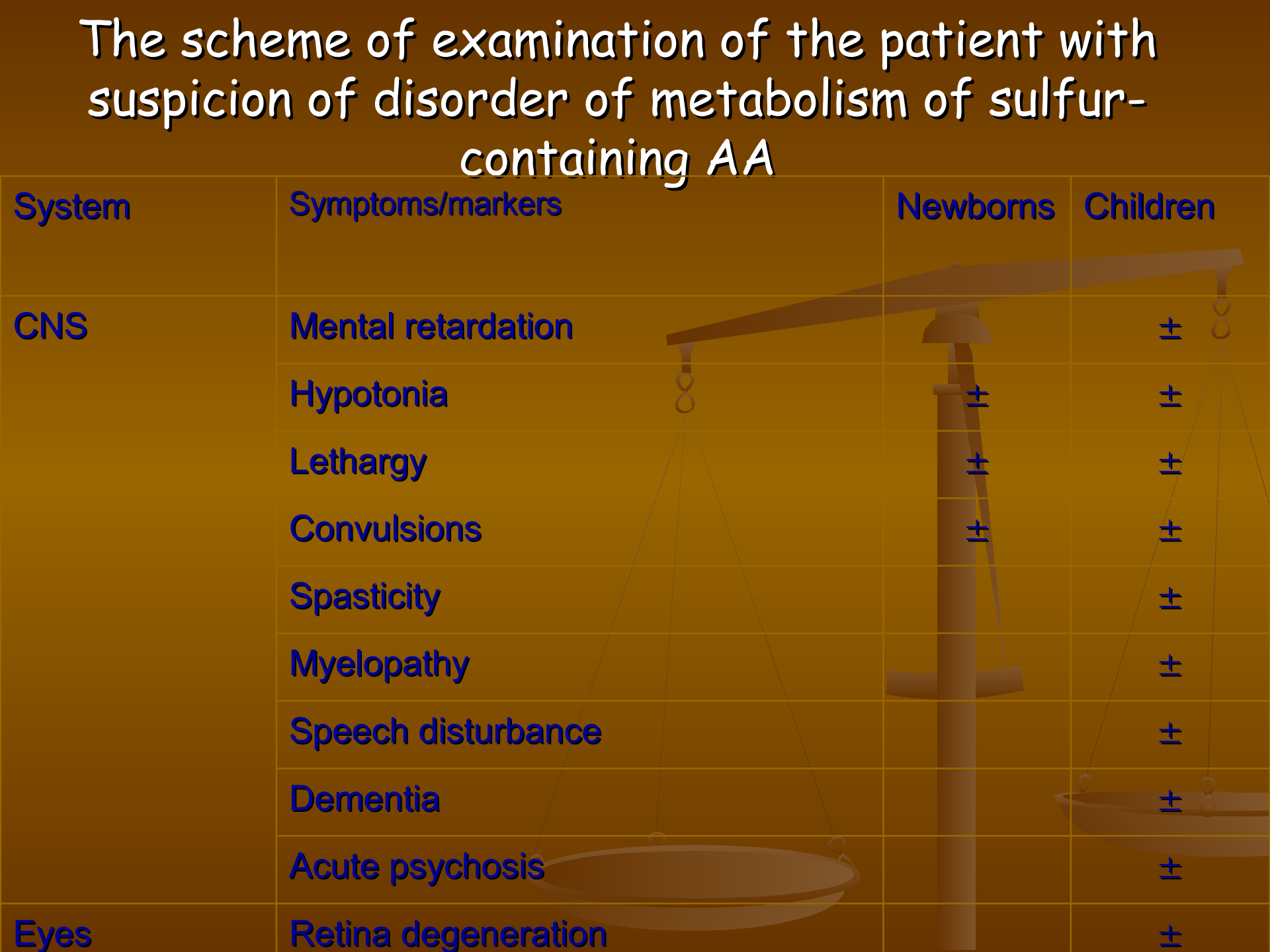


The scheme of examination of the patient with suspicion of disorder of metabolism of sulfur-containing AA

System	Symptoms/markers	Newborns	Children
Unique clinical signs	Development delay	±	±
	Behavioral disturbances	±	±
	Megaloblastic anemia		±
Special laboratory tests	Homocysteine (urine, blood)	↑	↑
	Methylmalonic acid (urine)	↑	↑
	Methionine (blood)	↓-norm	↓ -norm
Routine laboratory tests	Macrocytic anemia		±
	Hypersegments of neutrophils		±
	Thrombocytopenia		±

The scheme of examination of the patient with suspicion of disorder of metabolism of sulfur-containing AA

System	Symptoms/markers	Newborns	Children
CNS	Mental retardation		±
	Hypotonia	±	±
	Lethargy	±	±
	Convulsions	±	±
	Spasticity		±
	Myelopathy		±
	Speech disturbance		±
	Dementia		±
	Acute psychosis		±
Eyes	Retina degeneration		±



Characteristic deficiency of amino acids in autism

- According DAN theory: taurine is decreased and its intake is recommended in a high dose in chelation
- In statistical study of Moreno-Fuenmayor et al., performed in 1996 year,it was proved that 50% of children had an increased level of taurine, that was explained by compensatory character.

  Statistical study of 330 analyses in KhSMGC has shown its increase in 56% cases (that corresponds to serious study data), and its decrease only in 1 case.

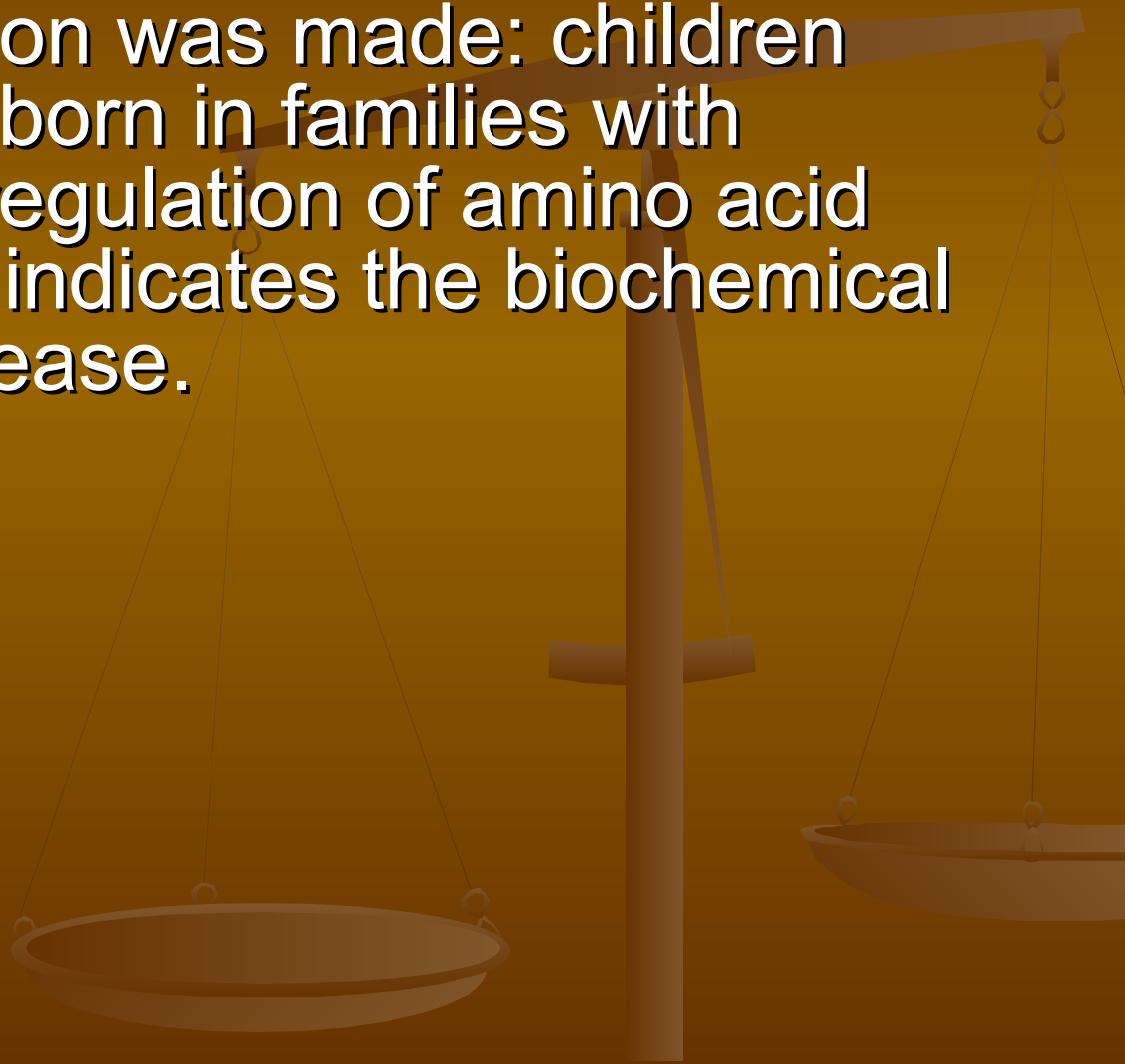
In considering other amino acids, DAN-theory is plastic in explanation (the decrease of amino acids in plasma, not connected with a diet, DAN-theory connects with two well-known effects of mercurous: inhibition of chorohydric acid development in ventricle, inhibition of various proteases and peptides, that creates problems for amino acid absorption, but self-confident in treatment: “tests can be not the best indicators, real test of therapy is more reliable”.

- DAN-theory recommends to increase the amount of proteins (proteins in food).
- Producers of BAA, more often using Bioshape and Protivity, also take part (isoleucine, methionine, valine, tryptophan, phenylalanine, lysine, valine), persuade the consumer in that there is no a single person, whom wasn't prescribed periodical intake of amino acids.

Examination of children older than 10 years, performed in 1996, showed that the concentration of glutamate and aspartate were appeared to be enough high, and glutamine and asparagine – low, the half of children had the increase of taurine.

There is a hypothesis that abnormality of glutamate levels can be caused by the presence high amounts of this amino acid in food, can have endogenic pattern (the result of disorder of metabolism of glutamate, receptor blockage and carrier function change).The increase of taurine concentrations, most probably, has compensatory pattern.

The conclusion was made: children with autism are born in families with disorder of the regulation of amino acid metabolism, tat indicates the biochemical basis of this disease.



- In I.S. Boksha’s opinion, 2005, such changes of amino acids correspond to glutamate neuromediate system and disorder (or change of synthesis speed) of the structure of neuromediate system components (receptors and carriers), including glutamate and cholinergic, serotonergic, dopaminergic, and also neuromediator metabolism play the key role in autism development.

- The decrease of essential amino acids is confirmed by studies (**G. Novarino et al,** 2012), this is explained by the mutation in BCKDK gene, which inactivates BCKD-kinase.

In our studies:

There is no decrease :

- Aspargine acid, glutamic acid, ammonia;

Increases of:

-lysine, methionine, leucine, tyrosine.

The most frequent decrease of :

- Valine, lysine, leucine, isoleucine, glutamine, tyrosine, phenylalanine, methionine, threonine (essential amino acids). It is corresponds to world studies

Increase of:

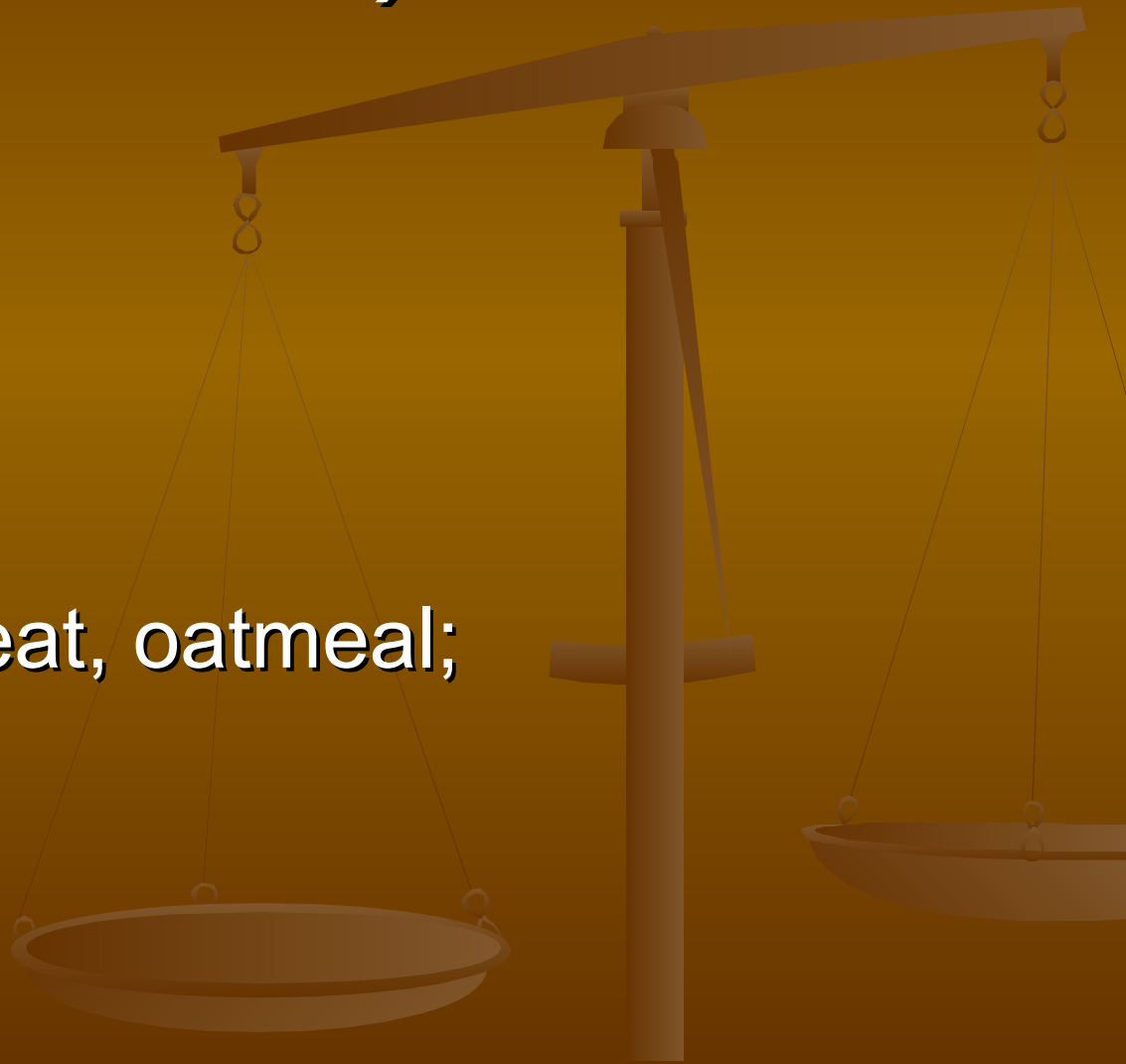
- Aspargine acid, glutamic acid, ornithine (replaced amino acids, excitatory neurotransmitters), ammonia. It is corresponds to world studies

It is recommended to restrict products (if glutamic acid is increased):

- Curd cheese;
- Eggs;
- Beef, chickens, pout;
- Porridges (except beech wheat, pea);
- Spaghetti;
- Bread (especially wheaten);
- Cookies

It is recommended to restrict products (if asparginic acid is increased):

- Eggs;
- Beef;
- Chickens;
- Pout;
- Rice, beech wheat, oatmeal;
- Corn cob;
- Pea



It is recommended to add to a diet (if there is deficiency of essential amino acids):

- Curd cheese and milk products ;
- Eggs;
- Beef, chickens, pout;
- Porridges (beech wheat, corn cob, pea);
- Spaghetti;
- Bread (especially wheaten);
- Cookies.

The treatment of disorders of AA metabolism depends on disease form and the clinical picture

- The most of these diseases respond to diet treatment by restriction of proteins and amino acids, involved in pathological process;
- Another therapeutic tactics, which is successful in treatment of hepatorenal tyrosinemia is inhibition of biochemical reactions, which precede metabolic block;
- Injection of high amounts of nicotinic acid – tryptophan cofactor (in the case of tryptophan deficiency in Hartnup disease);
- Prescription of penicillamine in cystinuria prevents renal colic by development of dissoluble disulfides with cysteine

In the periods of acute crisis, the following is recommended:

- Discontinuing of the ordinary diet;
- Often introduction of drinking in a great amount.

The frequency, amount, concentration of drinking depends on children age and the main disease.

- In urea cycle disorder it is necessary to increase medicines, which contribute to nitrogen release
- Carnitine is usually prescribed in organic acidemias.
- In disorder of branched chain-AA metabolism, their level can be decreased only because of protein formation; glucose polymers are injected for biosynthesis increase

- In phenylketonuria – a diet with a low content of phenylalanine
- Treatment diet is prescription of medicines influencing on amino acid metabolism: vitamins B, C, lipoic acid, organic acid, calcium, glycerophosphates, zinc-containing medicines
- For all groups of diseases – the necessity of the individual approach to the treatment of each child

The deficiency in autism by data of the world literature

- Metallothionein – a small protein, which is enriched with cysteine and is able to bind bivalent metals. The role of metalloprotein is the regulation of the concentration in the cell of these microelements, such as zinc and copper, and also in binding poisonous heavy metals, for example, cadmium and mercurous.

DAN! opinion

- 1. Metallothionein has to be reactivated and gradually renewed. That's why cysteine isn't ingested till zink and other bioelement drugs aren't prescribed for less than the term of 3-4 months. If metalloprotein is activated too quick, deterioration can be observed, because there is upload with heavy metals in circulation pathways.
- 2. Cysteine, which is necessary for metallothionein, acts the most effectively in the form of glutathione (GSH). It break downs in the intestine to cysteine with minimal side effects.
  3. Cysteine (GSH) in the combination with zinc and glutathione is the best way to remove excess copper and heavy metals.

- Glutathione (*2-amino-5-{[2-[(carboxymethyl)amino]- 1-(mercaptomethyl)-2-oxoethyl]amino}-oxopentanoic acid*, eng. *glutathione, GSH*) — is tripeptide γ-glutamyl cysteinyl glycine. Glutathione contains unusual peptide connection between amino group cysteine and carboxy-group of side chain of glutamate. The importance of glutathione in a cell is determined by its antioxidative properties. Glutathione not only defense a cell erom such toxic agents as free radicals, but also in the whole body determines redox-status of intracellular medium

- Alternatives of the use of glutathione include N-acetylcysteine, intravenous cysteine, lipoic acid. It can be appeared more effective method of the increase of glutathione level and that's why should be used under specialist follow-up
- Side effects:some children don't tolerate glutathione and can manifest temporary regress in behavior, especially if you began from a high dose. Nevertheless, the increase of glutathione level has significant meaning in the capacity of child's body to detoxify.

- ***Cysteine and cystine.***
- Can be bound with mercurous and thus release mercurous in blood again, deposited in tissues. Mercurous poisoning can be enhanced because of distribution of mercurous in other organs (possibly in brain).
- Wonderful nutrition medium for yeast infections.
- **Cysteine level in blood in autistic children can be high .**

- ***N-acetyl-L- cysteine (NAC)***
- Can be bond with mercurous and transfer it through cell membranes.
- Good nutrition medium for yeast infections
- Can quickly increase intracellular level of glutathione that is very useful for regeneration of antioxidant deficiency, but it is better to use in the combination with DMSA or after the release of mercurous from blood and tissues. Use carefully for children with a high level of cysteine

DAN! opinion

- 4. Metallothionein contains many sulfur residues. Injection of additional sulfur in the form of MSM can help in regeneration of the function of metallothionein in the intestine, liver, brain. Autistic children release sulfur (in urine) 2 times higher with urine comparing with normal children, and there is only 1/5 part of normal value in blood

DAN! opinion

- It is necessary to pay attention that autism transformation into the condition with emotional excitation can be in some cases. This can be explained by the fact that a quick increase of zinc in the intestine can lead to a quick synthesis of metallothionein, that temporary blocks zinc leading to expressed psychic excitation and hyperactivity. However, this is a sigh of regeneration!!!!

- 12. Additionally to cysteine, metallothionein contains 13 other amino acids. Many other autistic children aren’t able to break down proteins to amino acids necessary for synthesis of metallothionein. Introduction of amino acid complexes can be an important step in treatment process. It is necessary to avoid food cooked in microwave oven, because of protein denaturation and flavonoid breakdown.

Right DAN recommendations :

- When bioelement drugs are prescribed for regeneration of metallothionein function and a child responds (normal copper-zinc index in analyses) the following conclusion can be made: metallothionein function was degenerated.
  Methyl group deficiency is compensated by the use of methioneine, calcium, magnesium, vitamin B6. Calcium is very important for decrease of histamine level. Histamine hypomethylation makes normal its increase. Histamine acts as a mediator in brain.

From 150 children

Gender ratio was 1:3.5 (F:M), that corresponds to the world data. The main complaints were:

- - psycho-speech development delay– 100%;
- - the absence of visual contact and indicating gesture – 63%;
- - hyperactivity, aggression– 88%;
- - stereotypes – 85%;
- - stool disorders (constipations,predisposition to diarrhea) – 79%;
- - episyndrome – 22%
- - unusual body, urine, fecal masses, sweat odor – 34%;
- - frequent vomiting – 21%;
- - atypical dermatitis (frequently of unknown etiology and resistant to carried out hyposensibilized therapy) – 51%.

- By the time of manifestation:
- -the first year of life – 34%;
- -1-3 years– 66%.
- Parents connect disease onset:
- - vaccination – 31%;
- - infectious diseases with antibiotic therapy – 15%;
- - introduction of products with a high content of protein to the diet – 2%;
- - stress – 2%;
- -don’t connect with anything – 50%.

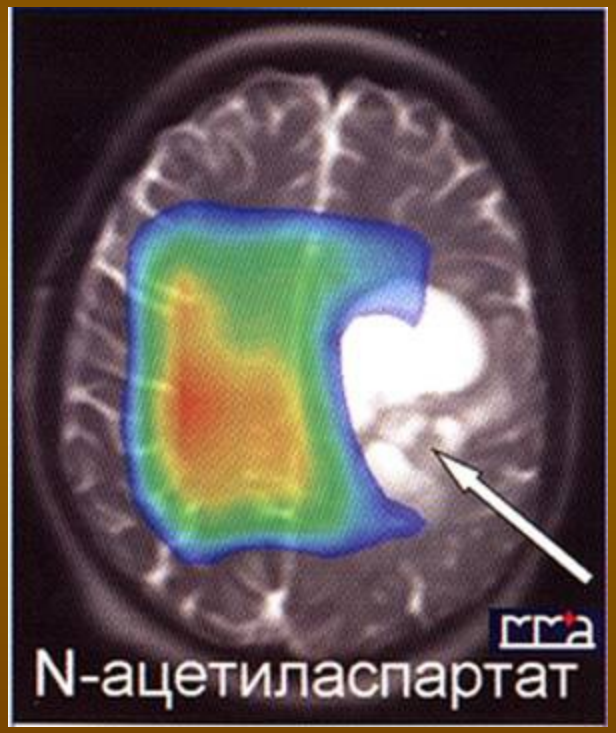
- Features of pregnancy and delivery course:
- -early toxicosis – 72%;
- - anemia – 22%;
- - threatened miscarriage and hormonal therapy – 47%;
- - pregnancy was with the help of EF – 3%;
- - genital tract infections– 49%;
- -ARVI, herpetic infection, flue – 69%;
- -weak delivery activity, stimulation– 66%;
- -quick delivery – 18%.

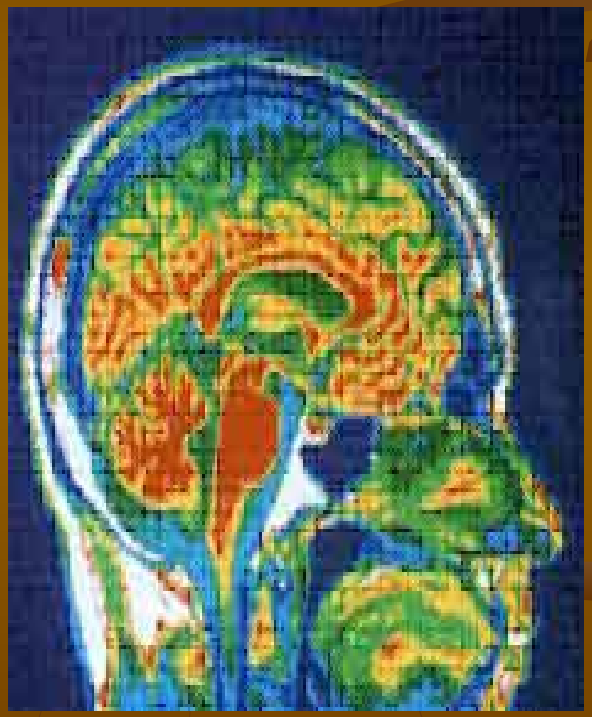
Features of newborn period:

- - prolonged conjugated jaundice – 33%;
- - perinatal CNS affection– 58%;
- - convulsive syndrome– 13%;
- - dysbacteriosis – 45%;
- - frank intertrigo – 10%.

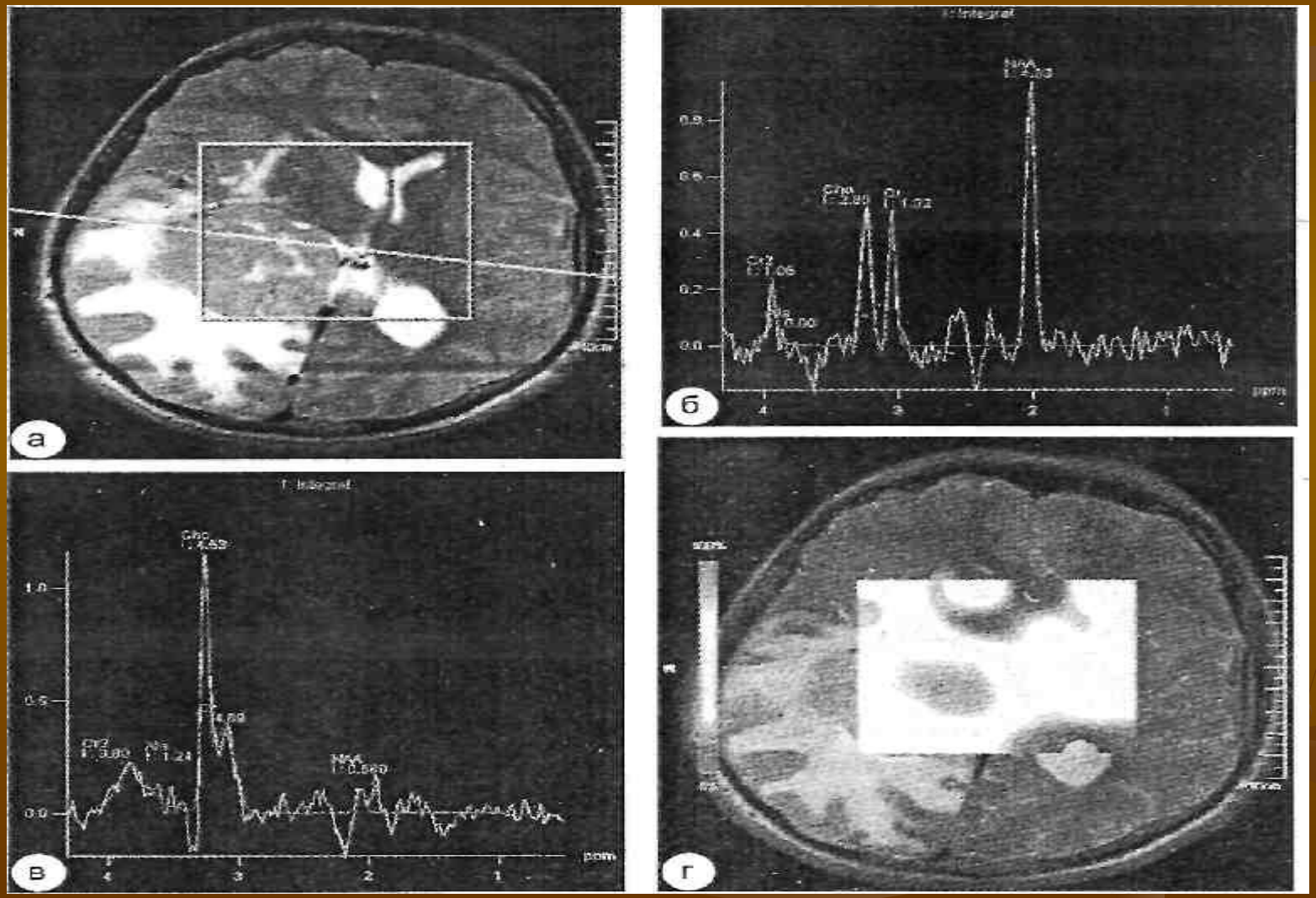
- Phenotype features:
- - surface location of subcutaneous veins– 88%;
- - paleness and dryness of skin– 90%;
- - marble skin– 74%;
- - hot pink palms – 87%;
- - atypical dermatitis– 34%;
- - skeletal changes (postural disorder,joint hypermobility, flat foot) – 76%.

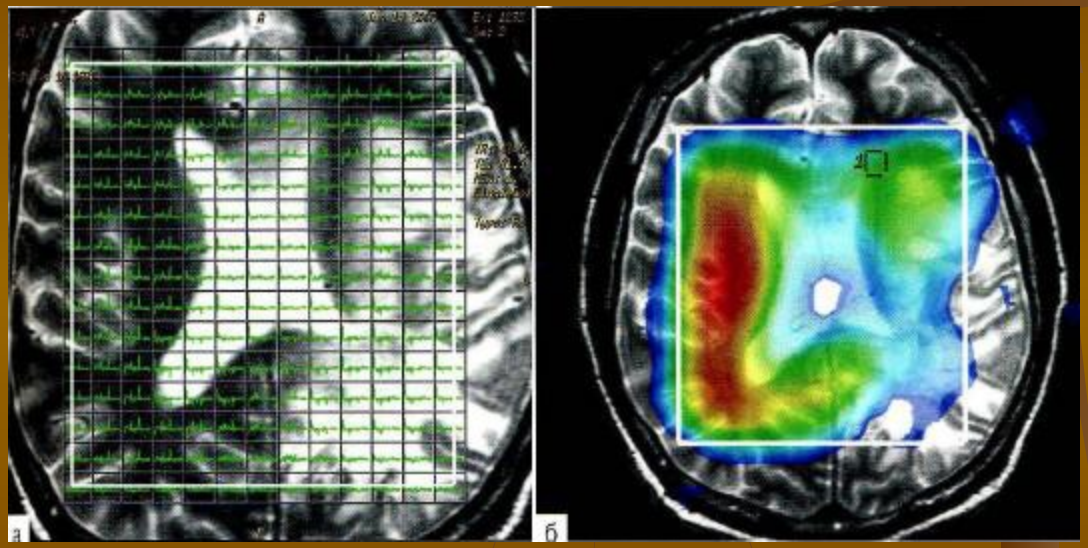
- Family history analysis:
- -cardiovascular pathology– 98%;
- - oncopathology – 75%;
- -diabetes mellitus– 34%.
- 14% of children kept to free-gluten and free-casein diet during consultation and examination.


NAA
N-ацетиласпартат



Proton (1H) MR-spectroscopy. Decrease of the content of N-acetylaspartate (NAA) (в) in meningioma (а), comparing with a normal spectrum in opposite side (б). (Trufanov, 2013)

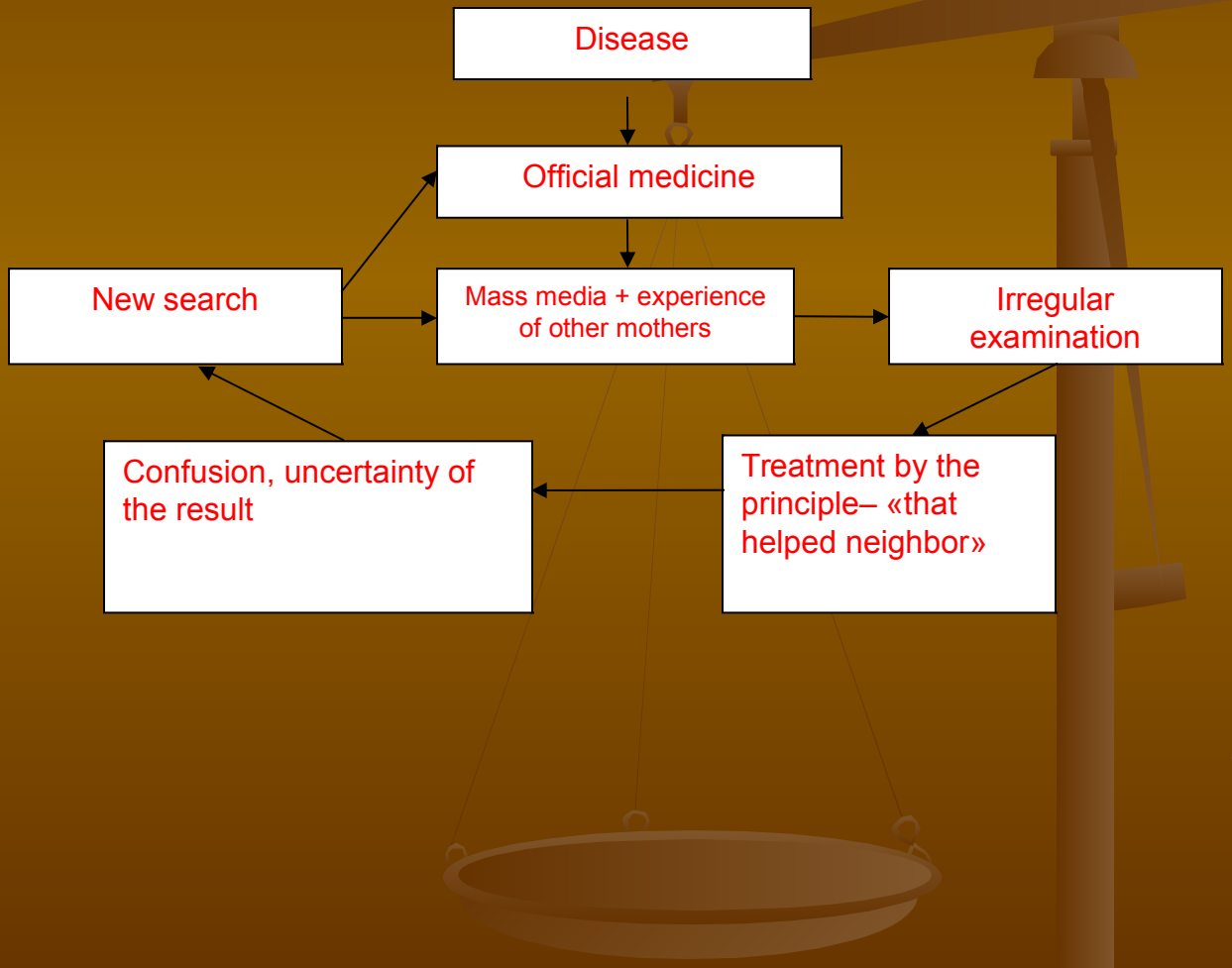



а
б

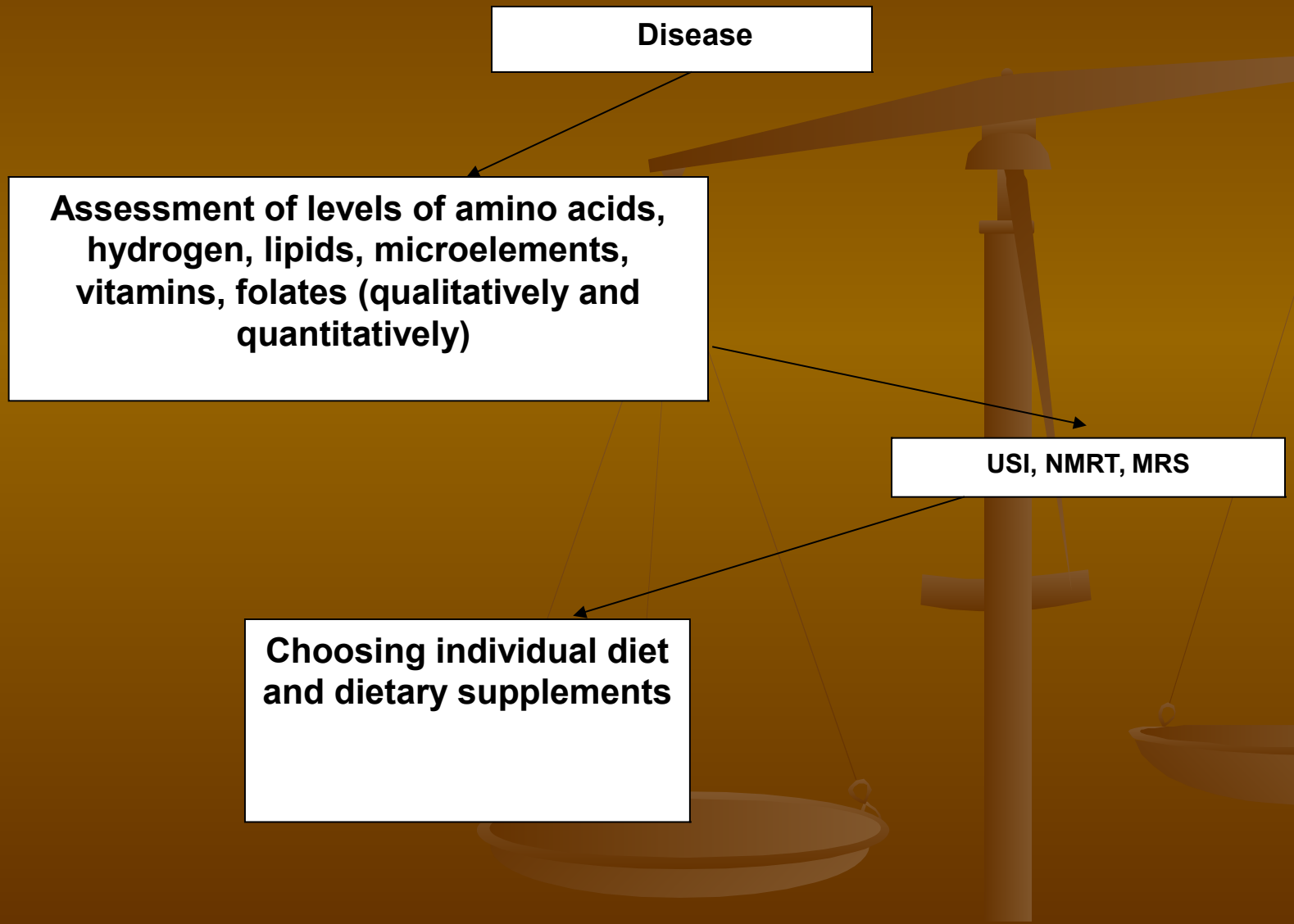
Our examination

- MRS: the child is hyperactive and aggressive. Conclusion: signals of N-acetylaspartate, creatine, choline, lactate, myoinositol are in spectrums. There are signals of **glutamate**, **glutamine and also lactate** in frontotemporal areas of the right hemisphere**.**

Mother's way


Disease
Official medicine
New search
Mass media + experience of other mothers
Irregular examination
Confusion, uncertainty of the result
Treatment by the principle– «that helped neighbor»

Recommended by the metabolic specialist way



WE CONFIRM MENTIONED DATA BY THE EXAMPLES OF OUR OBSERVATIONS

Diagnosis	**Differential diagnosis**				**Treatment**		**Effect**
	Biochemical	Molecular	Clinical	Diet therapy	Cofactor	Rehabilitation	
Schizophrenia+C677T MTHFR Hmzgt	+	+	+	+	+	+	recovery
Neurofibromatosis polymorphism		+	+	+	-	+	Long remission
Tuberous sclerosis polymorphism	+	+	+	+	-	+	Long remission of dispersion of tumors
Schizophrenia Disorder of tryptophan metabolism polymorphism	+	+	+	+	+	+	Full recovery
Dissecting myelitis 3 observations polymorphism	+	+	+	+	+	+	Recovery, return to work
Tuberous sclerosis polymorphism	+	+	+	+	-	+	Long remission. Return to work
Autism polymorphism	+	+	+	+	-	+	The child began to speak in 3 weeks after diet therapy

Thanks for your attention