
بسم الله الرحمن الرحيم

NEONATAL SCREENING FOR CONGENITAL METABOLIC DISEASES

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- What is congenital metabolic disease?

Congenital metabolic diseases or inborn errors of metabolism

- A  B

- Accumulation of substances which are toxic or interfere with normal function
- Reduced ability to synthesize essential compounds.

Classification of CMDs

- Intoxication
- Decreased energy production
- Decreased complex molecules

Intoxication

- Organic acidemies (propionic academia, Methylmalonic acidemia, Isovalertic academia)
- Aminoacidopathies (PKU, Tyrosinemia , MSUD,…)
- Urea cycle defects
- Metal intoxication (Hemochromatosis . Menkes , Wilson D)
- Sugar intolerance (Galactosemia, HFI)
- Porphyria
- Neurotransmitter defects

Intoxication

- Not interfere with the embryo-fetal development
- Present with a symptom-free interval
- Clinical signs of intoxication may be acute (vomiting, coma, liver failure, thromboembolic complications etc.)

or chronic (failure to thrive, developmental delay, ectopia lentis, cardiomyopathy etc.).

Energy production or utilization

- Deficiency in energy production or utilization within liver, myocardium, muscle, brain or other tissues.

Energy production or utilization

- Cytoplasm;

-Glycogen storage disease

- Gluconeogenesis defects

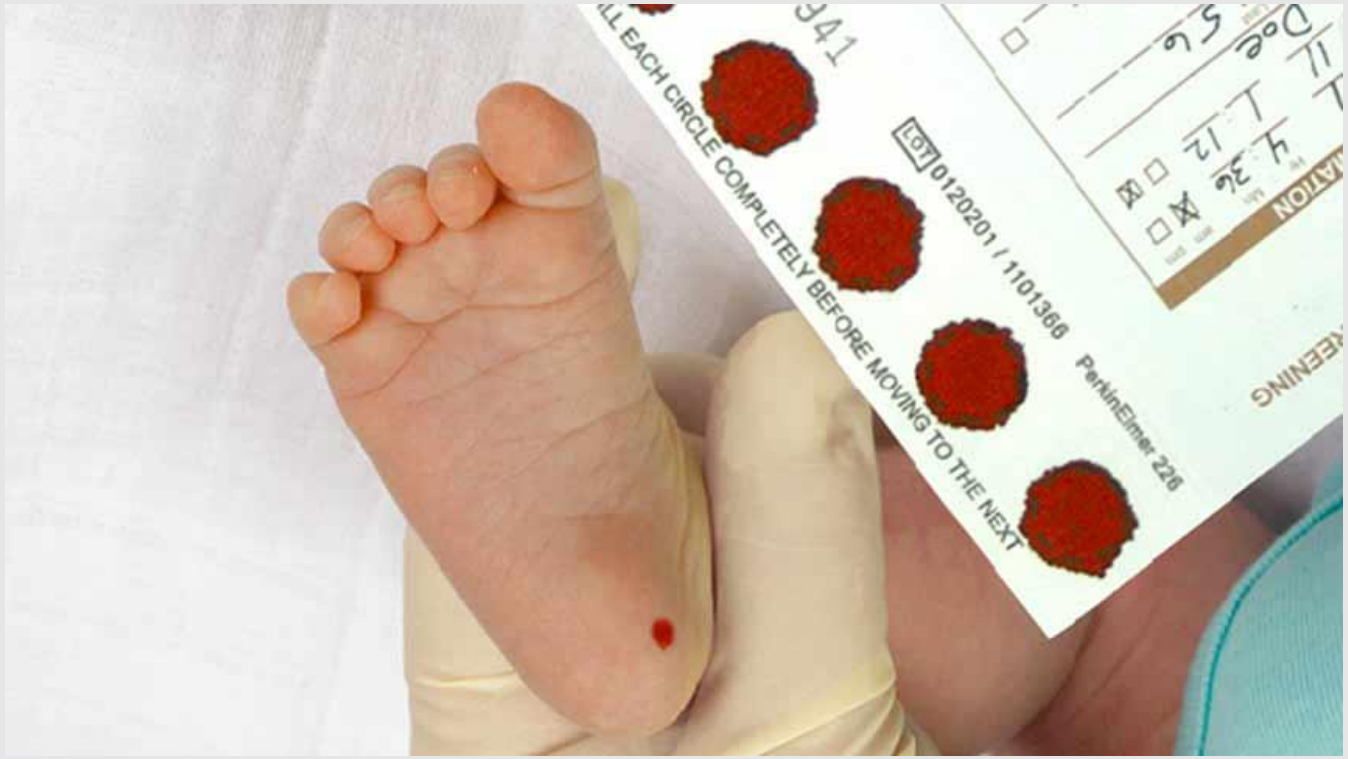
- Creatin transporter defects

- Mitochondrial diseases

Complex molecule defects

- Lysosomal storage diseases (Gaucher D , Neiman pick, Tay-sachs, …)
- Peroxisomal disorders (zellweger D. , Refsum D, …)
- Congenital Disorders of glycosylation

غربالگری نوزادان

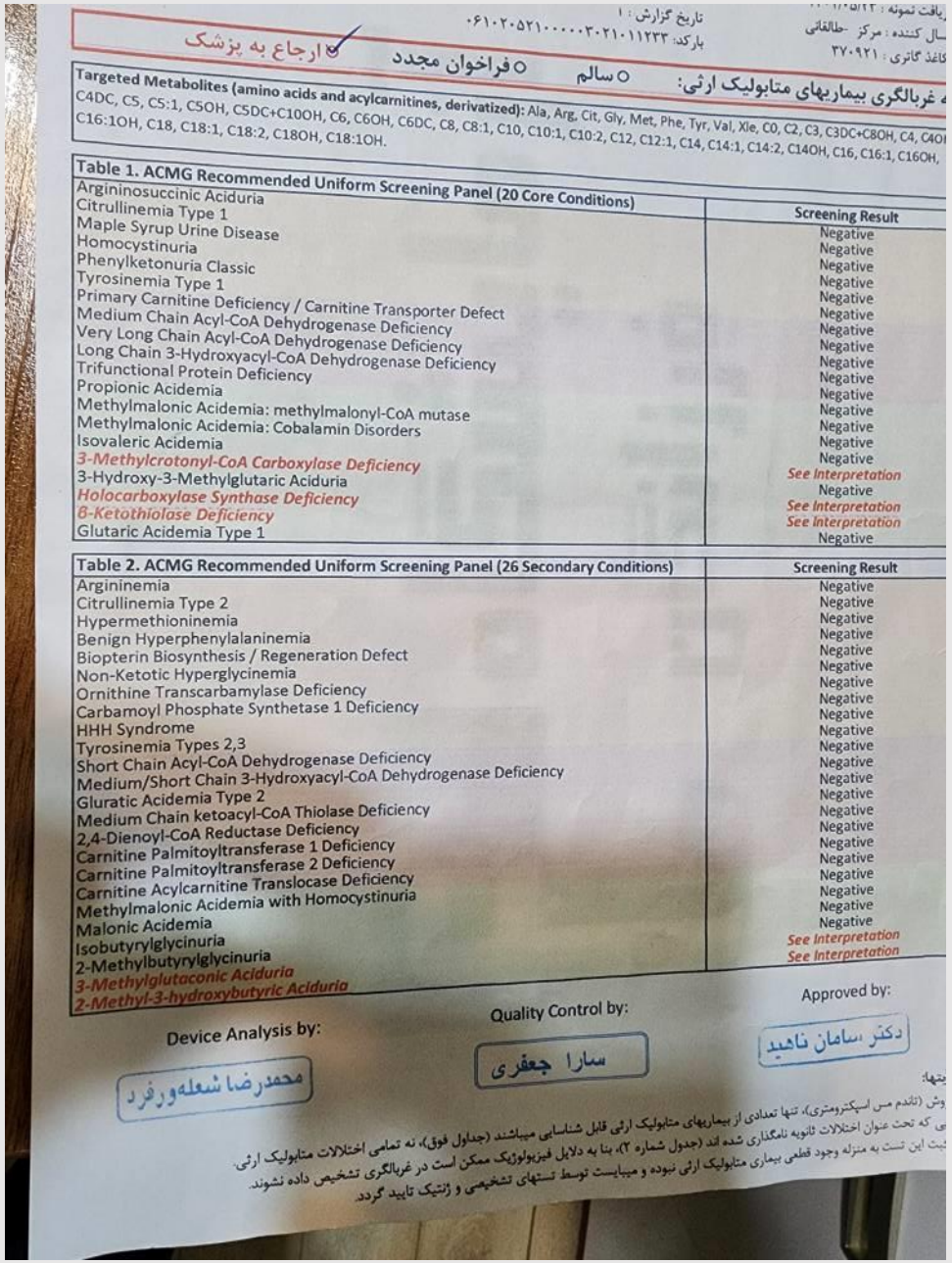


Neonatal screening for CMDs

- Dried Blood Spot
- 3^{rd}- 5^{th} day concomitant with TSH

Causes of abnormal screening results

- Nutritional problems
- Technical issues
- Maternal diseases or deficiencies
- Sepsis, prematurity,…
- Transient abnormalities
- False Positive results
- Congenital Metabolic Diseases



ارجاع به پزشک ✓ فراخوان مجدد ○ سالم ○ غربالگری بیماریهای متابولیک ارثی:

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سال کننده : مرکز -طالقانی
کاغذ گاتری : ۳۷۰۹۲۱

Targeted Metabolites (amino acids and acylcarnitines, derivatized): Ala, Arg, Cit, Gly, Met, Phe, Tyr, Val, Xle, C0, C2, C3, C3DC+C8OH, C4, C4OH, C4DC, C5, C5:1, C5OH, C5DC+C10OH, C6, C6OH, C6DC, C8, C8:1, C10, C10:1, C10:2, C12, C12:1, C14, C14:1, C14:2, C14OH, C16, C16:1, C16OH, C16:1OH, C18, C18:1, C18:2, C18OH, C18:1OH.

Table 1. ACMG Recommended Uniform Screening Panel (20 Core Conditions)	Screening Result
Argininosuccinic Aciduria	Negative
Citrullinemia Type 1	Negative
Maple Syrup Urine Disease	Negative
Homocystinuria	Negative
Phenylketonuria Classic	Negative
Tyrosinemia Type 1	Negative
Primary Carnitine Deficiency / Carnitine Transporter Defect	Negative
Medium Chain Acyl-CoA Dehydrogenase Deficiency	Negative
Very Long Chain Acyl-CoA Dehydrogenase Deficiency	Negative
Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	Negative
Trifunctional Protein Deficiency	Negative
Propionic Acidemia	Negative
Methylmalonic Acidemia: methylmalonyl-CoA mutase	Negative
Methylmalonic Acidemia: Cobalamin Disorders	Negative
Isovaleric Acidemia	Negative
3-Methylcrotonyl-CoA Carboxylase Deficiency	*See Interpretation*
3-Hydroxy-3-Methylglutaric Aciduria	Negative
Holocarboxylase Synthase Deficiency	*See Interpretation*
β-Ketothiolase Deficiency	*See Interpretation*
Glutaric Acidemia Type 1	Negative

Table 2. ACMG Recommended Uniform Screening Panel (26 Secondary Conditions)	Screening Result
Argininemia	Negative
Citrullinemia Type 2	Negative
Hypermethioninemia	Negative
Benign Hyperphenylalaninemia	Negative
Biopterin Biosynthesis / Regeneration Defect	Negative
Non-Ketotic Hyperglycinemia	Negative
Ornithine Transcarbamylase Deficiency	Negative
Carbamoyl Phosphate Synthetase 1 Deficiency	Negative
HHH Syndrome	Negative
Tyrosinemia Types 2,3	Negative
Short Chain Acyl-CoA Dehydrogenase Deficiency	Negative
Medium/Short Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	Negative
Gluratic Acidemia Type 2	Negative
Medium Chain ketoacyl-CoA Thiolase Deficiency	Negative
2,4-Dienoyl-CoA Reductase Deficiency	Negative
Carnitine Palmitoyltransferase 1 Deficiency	Negative
Carnitine Palmitoyltransferase 2 Deficiency	Negative
Carnitine Acylcarnitine Translocase Deficiency	Negative
Methylmalonic Acidemia with Homocystinuria	Negative
Malonic Acidemia	Negative
Isobutyrylglycinuria	*See Interpretation*
2-Methylbutyrylglycinuria	*See Interpretation*
3-Methylglutaconic Aciduria	
2-Methyl-3-hydroxybutyric Aciduria	

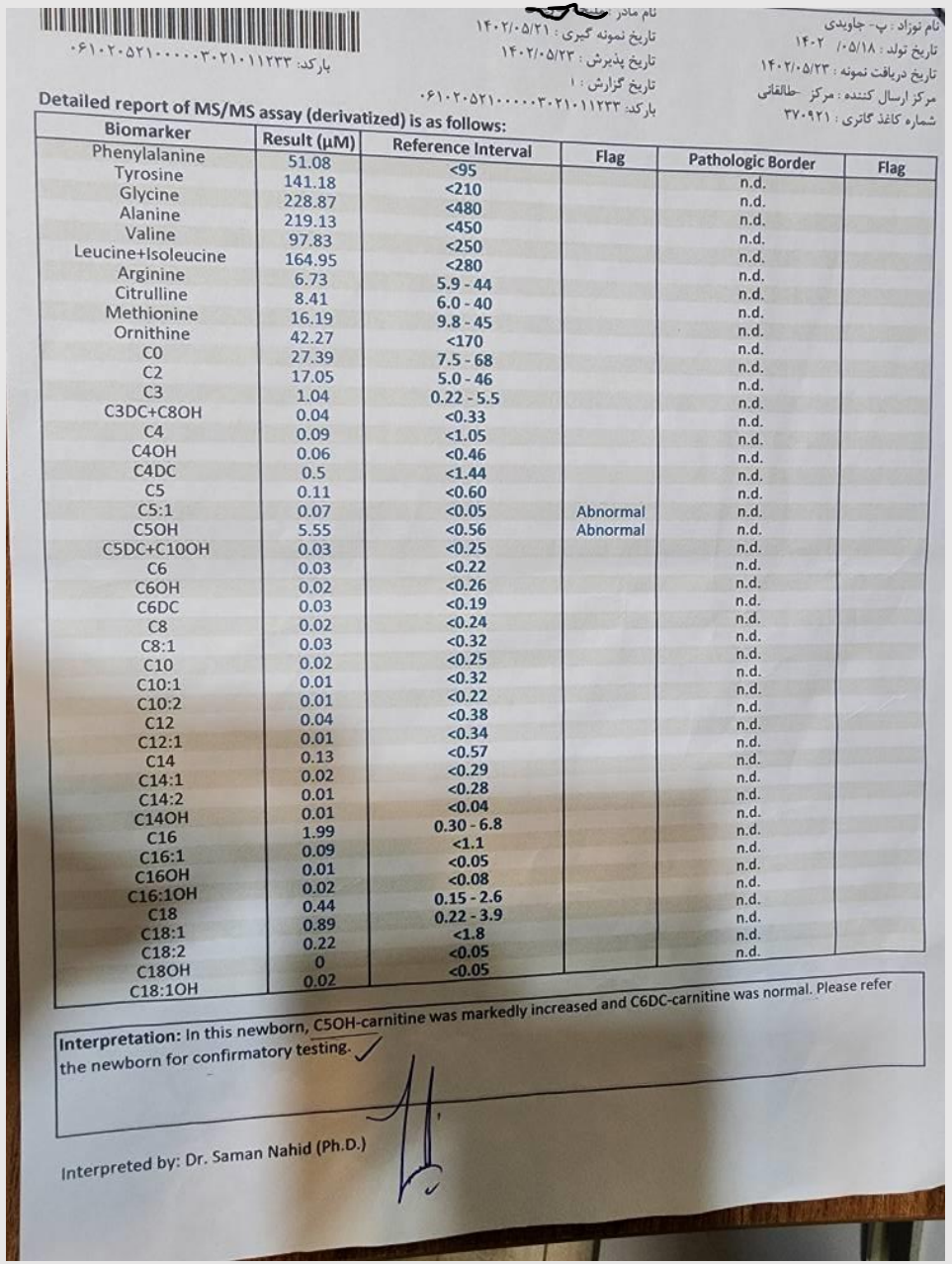
Device Analysis by: محمدرضا شعله‌ورفرد

Quality Control by: سارا جعفری

Approved by: دکتر سامان ناهید

یتها:

وش (تاندم مس اسپکترومتری)، تنها تعدادی از بیماریهای متابولیک ارثی قابل شناسایی میباشند (جداول فوق)، نه تمامی اختلالات متابولیک ارثی.
ی که تحت عنوان اختلالات ثانویه نامگذاری شده اند (جدول شماره ۲)، بنا به دلایل فیزیولوژیک ممکن است در غربالگری تشخیص داده نشوند.
ثبت این تست به منزله وجود قطعی بیماری متابولیک ارثی نبوده و میبایست توسط تستهای تشخیصی و ژنتیک تایید گردد.



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Detailed report of MS/MS assay (derivatized) is as follows:

Biomarker	Result (µM)	Reference Interval	Flag	Pathologic Border	Flag
Phenylalanine	51.08	<95		n.d.	
Tyrosine	141.18	<210		n.d.	
Glycine	228.87	<480		n.d.	
Alanine	219.13	<450		n.d.	
Valine	97.83	<250		n.d.	
Leucine+Isoleucine	164.95	<280		n.d.	
Arginine	6.73	5.9 - 44		n.d.	
Citrulline	8.41	6.0 - 40		n.d.	
Methionine	16.19	9.8 - 45		n.d.	
Ornithine	42.27	<170		n.d.	
C0	27.39	7.5 - 68		n.d.	
C2	17.05	5.0 - 46		n.d.	
C3	1.04	0.22 - 5.5		n.d.	
C3DC+C8OH	0.04	<0.33		n.d.	
C4	0.09	<1.05		n.d.	
C4OH	0.06	<0.46		n.d.	
C4DC	0.5	<1.44		n.d.	
C5	0.11	<0.60		n.d.	
C5:1	0.07	<0.05	Abnormal	n.d.	
C5OH	5.55	<0.56	Abnormal	n.d.	
C5DC+C10OH	0.03	<0.25		n.d.	
C6	0.03	<0.22		n.d.	
C6OH	0.02	<0.26		n.d.	
C6DC	0.03	<0.19		n.d.	
C8	0.02	<0.24		n.d.	
C8:1	0.03	<0.32		n.d.	
C10	0.02	<0.25		n.d.	
C10:1	0.01	<0.32		n.d.	
C10:2	0.01	<0.22		n.d.	
C12	0.04	<0.38		n.d.	
C12:1	0.01	<0.34		n.d.	
C14	0.13	<0.57		n.d.	
C14:1	0.02	<0.29		n.d.	
C14:2	0.01	<0.28		n.d.	
C14OH	0.01	<0.04		n.d.	
C16	1.99	0.30 - 6.8		n.d.	
C16:1	0.09	<1.1		n.d.	
C16OH	0.01	<0.05		n.d.	
C16:1OH	0.02	<0.08		n.d.	
C18	0.44	0.15 - 2.6		n.d.	
C18:1	0.89	0.22 - 3.9		n.d.	
C18:2	0.22	<1.8		n.d.	
C18OH	0	<0.05		n.d.	
C18:1OH	0.02	<0.05		n.d.	

Interpretation: In this newborn, C5OH-carnitine was markedly increased and C6DC-carnitine was normal. Please refer the newborn for confirmatory testing.

Interpreted by: Dr. Saman Nahid (Ph.D.)

Leucine + Isoleucine

Leucine + Isoleucine

Differential Diagnoses:

- MSUD
- Hydroxyprolinemoia
- Other rare IEM

Leucine + Isoleucine

- Urgent decision making
- Significant increase: may needs admission

Plan:

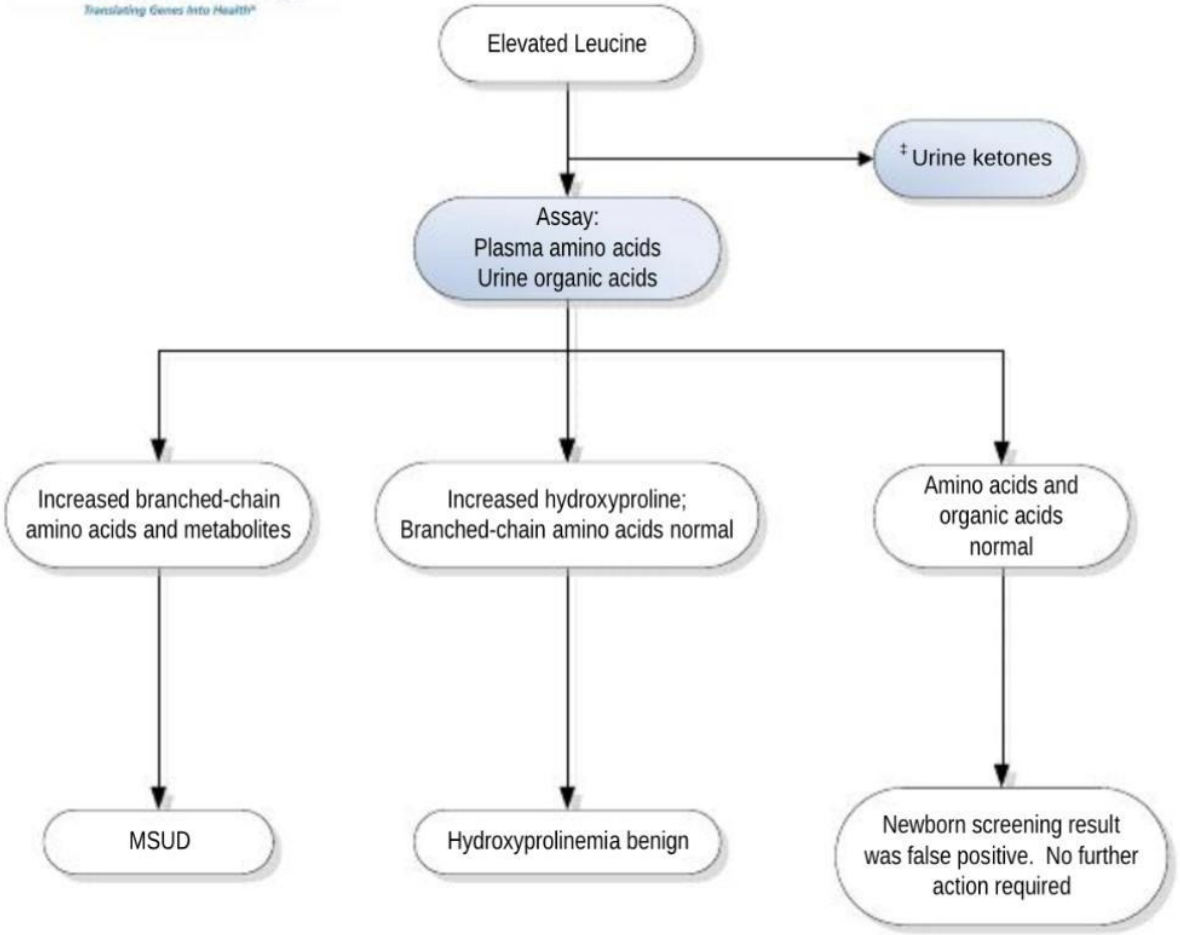
- Plasma aminoacids
- Urine organic acids
- Urine ketones

Decision making:

- Increased BCAA and metabolites: MSUD
- Allo-isoleucine is more specific
- Increased hydroxyproline, normal BCAA: benign hydroxyprolinemia
- Normal aminoacids and organic acids : reassurance, no further action

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

Leucine Elevated



REDUCED C0 (FREE CARNITINE)

Reduced C0 (free carnitine)

Differential Diagnoses:

- Carnitine uptake defect (primary carnitine def)
- Maternal carnitine deficiency
- Malnutrition
- Other metabolic diseases (glutaric aciduria1,…)

Reduced C0 (free carnitine)

Plan:

- Routine lab: (BS, electrolytes, VBG, CBC, ammonia)
- Plasma acyl carnitines
- Urine free carnitine (l-carnitine)
- Consider severity of abnormality

Reduced C0 (free carnitine)

Decision making:

- Normal plasma and urine carnitines: reassurance
- Decreased plasma l-carnitine (severe) and increased urine l-carnitine: carnitine uptake defect

HOW MANY PATIENTS WITH CMD ARE LIVING IN IRAN ?

- There is no accurate registry.
- About 500 diagnosed patients?
- About 150 diagnosed by neonatal screening

Are CMDs treatable?

- PKU
- Galactosemia
- Tyroinemia
- MSUD
- Gaucher
- Glutaric aciduria
- Cerebral Creatine Deficiencies
- Homocystinuria
- Methylmalonic acidemia

- What is the effect of early diagnosis of metabolic diseases on their prognosis?

PKU, Hyperphenylalaninemia

- CNS involvement
- Limitation of Phe in diet
- Calculation of dietary phe by parents
- Frequent measurement of Phe
- Novel methods of treatment by daily SQ injections
- Prognosis In cooperative patients is usually good

MSUD

- CNS involvement
- Limitation of Leucine, Isoleucine, Valine in diet
- Frequent measurement of plasma aminoacids
- Some patients have normal IQ

Tyrosinemia type 1

- Involvement of liver, kidney and nervous system
- Damage is caused by Succinyl acetone
- Treatment with Nitisinone to decrease succinyl acetone level
- Limitation of Tyrosine in diet
- Frequent measurement of LFT and succinyl acetone
- Disease can be controlled successfully.

Glutaric aciduria type 1

- CNS involvement
- Limitation of Lysine in diet
- L carnitine supplementation
- Some patients have normal IQ

Urea Cycle Defects

- CNS involvement
- Limitation of some aminoacids in diet
- Treatment with L.carnitine, Sodium Benzoate, Phenyl butyrate
- Frequent measurement of Ammonia
- Treatment can prevent or decrease CNS damage

Other Protein metabolism disorder

- Methylmalonic acidemia
- Propionic acidemia
- Isovaleric acidemia
- β-ketothiolase deficiency
- 3 Methyl crotonyl coa carboxylase deficiency
- Isobutyryl coa dehydrogenase deficiency

Special formula for each disease compensates for lack of protein consumption in that disease

Role of Pediatricians

- Psychosocial support
- Treatment may be difficult, but is beneficial.

Role of Pediatricians

- **Inborn errors of protein metabolism, acute illness:**
- Poor feeding, nausea, lethargy (even mild);
- Dextrose water, preferably 10% with Nacl, even in normoglycemia
- Stop dietary natural protein for 24-48 hr
- Increase L.carnitine dose 1.5-2 times
- Measure Ammonia level in Methylmalonic acidemia, Propionic acidemia, Isovaleric acidemia, Urea Cycle Defects and increase the dose of Na Benzoate and Phenylbutyrate is required

Fat metabolism disorder

- Primary Carnitine efficiency, Carnitine uptake defect
- Medium chain acyl coa dehydrogenase deficincy; MCAD
- Short chain acyl coa dehydrogenase deficincy; SCAD
- Other types

Primary Carnitine efficiency, Carnitine uptake defect

- Involvement of heart and muscles
- Treatment with high doses of L.carnitine
- Without treatment: lethal
- With treatment: Normal life

Fatty acid oxidation defects

- **MCAD def, SCAD def, VLCAD def:**
- Involvement of liver, heart, muscle and brain (hypoglycemia)
- Avoid fasting
- Without treatment: sudden cardiac death, CNS involvement
- With treatment: normal life

Galactosemia

- Screening only in Fars
- Liver involvement, Cataract
- Next years: renal involvement, delayed development especially speech delay, delayed puberty in girls
- Elimination of Galactose in diet (only dairy products)
- Without treatment: fulminant hepatic failure, cataract
- With treatment: Usually normal life

نکات کلیدی

- غربالگری نوزادان از نظر بیماری های متابولیک ارثی در روز ۳ تا ۵ تولد انجام می شود.
- تشخیص زودرس و درمان صحیح و به موقع می تواند زندگی نسبتا عادی را برای بیمار به ارمغان بیاورد.
- والدین این بیماران کار سختی به عهده دارند. نیاز به انگیزه و روحیه دارند.
- درمان صحیح و فوری بیماران در هنگام بیماری و عفونت بسیار حیاتی است.


THANK YOU
FOR YOUR
ATTENTION