대한 유전성 대사 질환 : 2014;14(2):123~134

종 설

유전성대사이상질환의 진단의 체계적 접근

한림대학교 의과대학 소아청소년과학교실

이 홍 진

Systematic Approach for the Diagnosis of IEM

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Recent advances in the diagnosis and treatment of inborn errors of metabolism (IEM) have improved substantially the prognosis of many of these diseases, if diagnosed early enough before irreversible damage occurs. Diseases of inborn errors of metabolism are so diverse over several hundred disease up to now and may be several thousand in near future, and these diversities of IEMs make clinicians embarassed. The signs of neurological dysfunctions of many IEMs manifesting in the neonatal period is very nonspecific, such as poor feeding, poor sucking, apnea or tachypnea, vomiting, hypertonia, hypotonia, seizure, letharginess, consciousness change and coma. But after neonatal period, the signs of neurological deficits become specific and localized. The results of routine basal laboratory tests such as metabolic acidosis, hyperammonemia, lactic acidemia, ketonemia or hyperuricemia can give very important clinical clues for the diagnosis of IEMs. Even no abnormal findings on routine laboratory test could be very important clue for NKH, sulfite oxidase deficiency and peroxisomal disorders. These various clinical manifestations of these diverse diseases can be categorized and summarized. This makes it essential that the practicing clinicians be familiar with the clinical presentations and symptomatic and systematic approaches of these disorders. Characteristic clinical presentations, methods of symptomatic and systematic approach and typing of various disorders is discussed in this review.

Kew words: Inborn errors of metabolism. IEM, Systematic approach, Symptomatic approach

Introduction

There have been common worldwide misconceptions about IEM for long that has made doctors hate thinking about IEM. First of all you should know the complex pathways to treat a patient with IEM that ailed him as a student but to know pathway is not obligatory, only optional and diagnosis and treatment of nearly all IEMs can be done that you do not know the exact pathways. The second thing is that IEMs are very rare, so they should be diagnosed after perfectly ruled out common diseases especially infectious diseases. This is a paradigm of partially correct in fact that they commonly co-manifest with infection. Infection make hypercatabolic status that aggravate IEMs and in vice versa IEMs commonly lowers immunity and can cause infection. You

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should think of both conditions simultaneously. The third thing is that it's hard to make money that is also partially true. Diagnostic work ups to rule out IEMs could give you a economical opportunities. The fourth thing is that there is no treatment for IEMs, but recently various modalities of treatment such as ERT, organ transplantation (BM, liver etc.), cell therapy, gene therapy have gotten great improvement for clinical use. In Korea, marriage between same subfamily name had been prohibited by law about 600 years and that makes the incidence of recessive disorders markedly but the law has been abandoned several years ago[1].

The most embarrassing thing for the doctors who have interest on IEM is that diseases of IEM are so diverse over several hundred disease up to now and may be several thousand in near future. The signs of neurological dysfunctions of many IEMs manifesting in the neonatal period is very nonspecific, such as poor feeding, poor sucking, apnea or tachypnea, vomiting, hypertonia, hypotonia, seizure, letharginess, consciousness change and coma. But after neonatal period, the signs of neurological deficits become specific and localized [2]. The results of routine basal laboratory tests such as metabolic acidosis, hyperammonemia, lactic acidemia, ketonemia or hyperuricemia can give very important clinical clues for the diagnosis of IEMs[3, 4]. Even no abnormal findings on routine laboratory test could be very important clue for NKH[5], sulfite oxidase deficiency and peroxisomal disorders. These various clinical manifestations of these diverse diseases can be categorized and summarized. This makes it essential that the practicing clinicians be familiar with the clinical presentations and symptomatic and systematic approaches of these disorders.

The clinical manifestations of IEMs depends on the level of residual enzyme activity. If a mutation makes residual enzyme activity nearly zero, symptoms and signs start early on neonatal period or infantile period and called classical or typical form, but if there's some residaual enzyme activity of about 10-20%, he can live a healthy life until later and called juvenile onset or adult onset form. For organic acidopathies and fatty acid oxidation disorders, sudden aggravation of symptoms and signs on a stressful hypercatabolic status and Reye-like illness or recurrent reye-like illness[6]. On acute hypercatabolic episode, the clinical manifestations and laboratory findings are same as classical form but rapidly normalized on treatment and could be a source of missing diagnosis. So if there's any possibilities of IEM on initial history takings and physical examinations, samples for confirmatory diagnostic tests should be stored on refriegerator or freezer.

Case presentations

Case 1

4 days old male neonate visited ER with the CC of sudden onset vomiting, poor feeding and letharginess. He was born as NFSD, with birth weight of 3.5 kg. There has been no problems after birth, with active sucking, active spontaneous movement, good muscle power until the initiation of symptoms. On physical examination at ER, liver was 2 FB palpable below Rt. subcostal margin, muscle power and tone was decreased markedly and normal neonatal reflexes such as Moro, rooting and sucking were decreased markedly. Routine laboratory tests showed pH: 7.15, CBC: 5,500-12.0-25.6-200K, Ammonia: 350 mg/dL, GOT/

GPT: 150/200 IU/L, Lactate/pyruvate: 5.6/1.5 mmol/L. Under the impression of organic acidopathies, urine organic acid analysis was done and showed Lactic acid: 550 (7–150 mmol/mol Cr), 3–OH–propionic: 1,500 (2–15 mmol/mol Cr), 3–Hydroxybutyric: 1,200 (0–15 mmol/mol Cr), Acetoacetic: 900 (0–10 mmol/mol Cr), Methylmalonic: 5 (0–7 mmol/mol Cr), Propionylglycine: 1,300 (0 mmol/mol Cr), Methylcitric: 950 (0–15 mmol/mol Cr) and diagnosis was propionic acidemia, classical form.

Case 2

4 days old female neonate visited ER with the CC of sudden onset vomiting, poor feeding and letharginess. She was born as NFSD, with birth weight of 3.5 kg. There has been no problems after birth, with active sucking, active spontaneous movement, good muscle power. On physical examination at ER, liver was 2 FB palpable below Rt. subcostal margin, muscle power and tone was decreased markedly and normal neonatal reflexes such as Moro, rooting and sucking were decreased markedly. Routine laboratory tests showed pH 7.50, CBC: 5500–12.0–25.6–200K, Ammonia: 1,500 mg/dL, GOT/GPT: 150/200 IU/L, Lactate/pyruvate: 7.5/3.0 mmol/L. Organic acid analysis and aminoacid analysis was done and showed Lactic acid: 600 (7–150 mmol/mol Cr), 3–Hydroxybutyric: 1,000 (0–15 mmol/mol Cr), Acetoacetic: 1,000 (0–10 mmol/mol Cr), Orotic: 1,000 (0 mmol/mol Cr). Glutamine and alanine were elevated and citrulline, argininosuccinate and arginine were decreased and diagnosis was ornithine transcarbamylase deficiency.

Case 3

4 Year old girl visited ER with the CC of seizure and consciousness change. On PMH, there has been no specific problem until recently. 4 Days PTV, high fever and sore throat developed and she have eaten nearly nothing after then. 2 Days PTV, vomiting developed and seizure and consciousness change followed. On physical examination, there was no meningeal irritation sign. On CSF examination, no pleocytosis detected but pressure was elevated (over 18 Cm H_2O) and protein was elevated (50 mg/dL). On LFT, glucose was low (20 mg/dL), GOT/GPT was elevated (350/400 IU/L). Ammonia was elevated up to 500 mg/dL. pH Was 7.20. To Rule out Reye syndrome, late onset organic acidemias, late onset urea cycle disorders, fatty acid oxidation disorders, and urine organic acid analysis and plasma aminoacid analysis showed Lactic acid: 800 (7–150 mmol/mol Cr), 3–OH–propionic: 1,200 (2–15 mmol/mol Cr), 3–Hydroxybutyric: 1,000 (0–15 mmol/mol Cr), Acetoacetic: 1,000 (0–10 mmol/mol Cr), Methylmalonic: 8 (0–7 mmol/mol Cr), Propionylglycine: 1,300 (0 mmol/mol Cr), Methylcitric: 1,500 (0–15 mmol/mol Cr), and diagnosis was propionic acidemia, intermediate form.

Case 4

6 year old boy visited ER with the CC of afebrile seizure. He has been treating as URI due to rhinorrhea, cough, and sputum for 2 days at a private clinic. On P/E, L/R: prompt, isocoric, N/S: negative, N/E: Lethargic state, muscle power was relatively preserved, and sensory was intact. On routine laboratory tests, VBGA (pH– PCO_2^- PO_2^-

BE) was 7.18-43 mmHg-96 mmHg-11.8 mmol/L, Glucose: 8 mg/dL, Ammonia: 429 mmol/L, AST/ALT (IU/L) 65/19, i-Ca: 1.12 mmol/L, WBC-Hgb-Plt: 23,400-10.9-773,000. CSF study showed pH: 7.5, S.G: 1.004, Cell count: RBC 0, WBC 0, Chemistry: Protein 19 mg/dL, Glucose 49 mg/dL. To Rule out Reye syndrome, late onset organic acidemias, late onset urea cycle disorders, fatty acid oxidation disorders, and urine organic acid analysis and plasma aminoacid analysis showed Lactic: 145 (7-150 mmol/mol Cr), 3-Hydroxybutyric: 3,987 (0-15 mmol/mol Cr), 3-Hydroxyisovaleric: 559 (2-20 mmol/mol Cr), Ethylmalonic: 384 (1-20 mmol/mol Cr), Acetoacetic: 2,726 (0-10 mmol/mol Cr), Glutaric: 201 (0-15 mmol/mol Cr), Isobutyrylglycine: 389 (0-1 mmol/mol Cr), 2-Hydroxyglutaric: 2,910 (5-110 mmol/mol Cr), Isovalerylglycine: 237 (0-2 mmol/mol Cr). Follow up urine organic acid analysis after 24 hours IV glucose treatment showed markedly decreased (Lactic: 232, 3-Hydroxybutyric: 21, 3-Hydroxyisovaleric: 7, Ethylmalonic: 58, Acetoacetic: 14, Glutaric: 3, Isobutyrylglycine: 0, 2-Hydroxyglutaric: 477, Isovalerylglycine: 2). Diagnosis was Glutaric aciduria type II, mild form.

Case 5

12 year old girl visited OPD with the CC of abnormal eye movement. On P/E, she showed choreoathetoid movement, hepatosplenomegaly. On CBC, severe anemia and thrombocytopenia detected. On imaging procedures, huge hepatosplenomegaly, rare factions of femur, Erlenmyer flask deformity of distal femur, avascular necrosis of femur head and flatyspondyly were detected. On BM examination, specific macrophage was detected and confirmed as Gaucher disease with enzyme study and molecular study.

Case 6

8 year old boy visited OPD with the CC of intermittent severe pain of foot, aggravated on exercise and high temperature. On P/E, no Jt. swelling detected and multiple angiokeratoma on inguinal area and buttock visible. On slit lamp examination, whirl like corneal clouding visible. On audiometry, there was sensorineural hearing loss of high tone. On urinalysis there was moderate proteinuria. Hypertrophic cardiomyopathy was detected on 2-D echocardiography. Urine GL-3 was markedly elevated and enzyme assay and molecular study confirmed Fabry disease.

Symptomatic approaches

Systematic approaches for the diagnosis of IEM is very important and as follows: History Taking, Physical Examinations, Routine Laboratory Tests, Biochemical Screening Tests, Biochemical Confirmatory Tests, Pathologic Studies, Molecular Studies. Diseases of IEM were very diverse but they showed relatively narrow and specific spectrum of symptoms and signs that makes symptomatic and systematic approach for the diagnosis of IEM possible.

On family history, dominant disorders, recessive disorders and mitochondrial disorders showed specific patterns. many mitochondrial respiratory chain disorders showed chracteristic maternal Inheritance pattern. Personal past medical history is also very important, especially if he or she had chronic progressive disorders or recurrent episodes; recurrent Reye-like illness. On physical examination, hepatomegaly, splenomegaly, cardio-

megaly, glossomegaly, gait disturbance, movement disorders (choreoathetosis or tremor) and angiokeratoma should be emphasis.

From now on, some symptoms and signs of clinical importance with possible diagnosis of IEM will be presented.

Alopecia, Brittle hair
- Menke's kinky hair disease
- Argininosuccinic aciduria
- Lysinuric protein intolerance
- Homocystinuria
- Multiple carboxylase deficiency[7)]
- Acrodermatitis enteropathica

Anemia
- Organic acidemias: BM suppression[8)]
- Lysosomal storage diseases: hypersplenism
- Pyroglutamic aciduria: Hemolytic anemia
- Dihydrofolate reductase defieicncy: Megaloblastic anemia
- Cholesteryl ester storage disease: GI blood loss

Angiokeratomatosis
- Fabry disease[9)]
- Fucosidosis
- Sialidosis

Ataxia
- Organic acidemias–Mild late onset form: MMA, MSUD, 3–MGLTC, Hyperargininemia, Biotinidase def., GA I
- Mitochondrial disorders[10)]: Leigh SNE, Complex I def., Complex III def., PDHC def.[11)], PC def.[11)]
- Lysosomal storage diseases: MLD, GM1, GM2, ML I, Fucosidosis
- Peroxisomal disorders: Refsum disease

Bony Abnormalities
- Arthritis, Arthralgia: Gout, Hyperoxaluria I, II, Gaucher, Alkaptonuria, Farber
- Dysostosis multiplex, Coarse facial feature: MPS, ML, Oligosaccharidosis
- Marfanoid phenotype: Homocystinuria I
- Prolidase def.
- A–Aminoadipic aciduria

Cardiomyopathy, Cardiomegaly
- Mitochondrial disorders: Complex III def., Complex IV def.
- Fatty acid oxidation disorders[12)]
- Mucopolysaccharidosis: MPS IH, IS, II
- Oligosaccharidosis: Fucosidosi
- Pompe disease: Infantile form
- Fabry disease
- Ethanolaminosis

Corneal clouding, Cataract
- MPS IH
- Mannosidosis
- Galactosemia
- Fabry disease
- Homocystinuria I
- Cystinosis
- Refsum disease[13)]
- Cross syndrome

Cherry red spot
- Nieman Pick disease
- Tay Sachs disease
- Sandhoff disease
- GM1 gangliosidosis
- Mucolipidosis I
- Krabbe disease

- Sialidosis I

Liver cirrhosis
- Tyrosinemia I
- Galactossemia
- Wilson disease
- GSD I, IV, VI

Coarsening of facial feature
- Mucoplysaccharidosis: I, II, III, IV, VI
- Oligosaccharidosis: Mannosidosis, Fucosidosis
- Mucolipidosis II
- GM1 gangliosidosis
- N-Aspartylglucosaminuria

Coma, Consciousness change
- Urea cycle disorders
- Organic acidemias
- Mitochondrial disorders
- Nonketotic hyperglycinemia
- Fructose-1,6-diphosphatase def.
- Hereditary fructose intolerance

Dementia
- Mitochondrial disorders: Leigh SNE, Complex I def., Complex II def.
- Lysosomal storage disease: Gaucher II, III, Nieman Pick ds
- Mucopolysaccharidosis: MPS IH
- Leukodystrophies: MLD, ALD, Krabbe, Alpers, Neuronal ceroid lipofuscinosis

Developmental delay
- Mitochondrial disorders: Leigh SNE, Complex I def., Complex II def., PDHC def., PC def.
- Lysosomal storage disease: Gaucher II, III, Nieman Pick ds, GM1
- Mucopolysaccharidosis: IH, III, VIII
- Oligosaccharidosis: Mannosidosis, Fucosidosis
- Fatty acid oxidation disorders
- Homocystinuria
- Tyrosinemia I
- Arginase def.

Diarrhea
- Congenital chloridorrhea
- Disaccharidase deficiency
- Galactossemia
- GSD I
- Hereditary fructose intolerance
- Tyrosinemia
- Lysinuria protein intolerance
- Wolman disease
- Pyroglutamic acidemia

Dysarhtria, Slurred speech
- Methylmalonic aciduria (Cbl C, Cbl D)
- 3-Methylglutaconic aciduria
- Histidinemia
- a-Glutamyl cystein synthetase def.
- GM2 gangliosidosis, juvenile
- GM1 gangliosidosis with normal intelligence
- MLD
- ALD
- Neuronal ceroid lipofuscinosis

Fatty degenertion of Liver
- Glutaric acidemia II
- Hereditary fructose intolerance
- Galactossemia (UT def.)
- Fructose-1,6-diphosphatase def.[14)]
- Reye syndrome

Hearing loss (Sensorineural)
- Prolinemia
- Fabry ds

- Mitochondrial disorders: Complex I def., Complex III def.
- Mucopolysaccharidosis: MPS II, MPS IV
- Mannosidosis
- Zellweger syndrome
- Metachromatic leukodystrophy
- Waardenburg syndrome
- Alport syndrome

Hepatomegaly
- Lysosomal storage disorders: Sphingolipidosis, Mucoplysaccharidosis, Oligosaccharidosis, Mucolipidosis
- Disorders of CHO metabolism: Glycogen storage diseases, Galactossemia, Hereditary fructose intolerance
- Disorders of AA: Urea cycle disoders, Organic acidemias
- Zellweger syndrome

Splenomegaly
- Sphingolipidosis: NP, Gaucher, GM1, GM2, Farber, Wolman
- Mucopolysaccharidosis: All type except IS, IV
- Oligosaccharidosis: Mannosidosis, Fucosidosis
- Mucolipidosis I
- Prolidase def.
- Galactosemia (UT def.)
- GSD II, IV
- Chediak Higashi syn

Hyperacusis
- GM1 gangliosidosis
- GM2 gangliosidosis, Type I
- GM2 gangliosidosis, Type II

Hyperactive syndrome
- PKU
- MPS III
- Neuronal ceroid lipofuscinosis

Hypertonia (Spasticity)
- Glutaric aciduria type I
- Arginase def.
- Maple syrup urine disease
- Homocystinuria III
- GSD III
- Gaucher type 2
- GM2 gangliosidosis
- Fucosidosis
- Leigh SNE, PDHC def.
- Leukodystrophies: MLD, Krabbe, Canavan, Neuronal ceroid lipofuscinosis

Hypotonia
- Werdnig Hoffman ds
- Organic acidemias: Propionic acidemia, HMG CoA lyase def, 3-Methylcrotonylglycinemia, Holocarboxylase synthetase def., Pipecolic acidemia, Ethanolaminosis
- Glycogen storage diseases: Ia, II, III, VIII
- Lysosomal storage diseases: Nieman Pick, GM1, GM2, ML II, ML IV, Mannosidosis, MLD
- Peroxisomal disorders: Zellweger syndrome
- Mitochondrial disorders: Complex I def, Complex IV def., Leigh SNE, Fumarase def, PDHC def., PC def.

Hypohydrosis
- Fabry ds
- Familial dysautonomia

Macrocephaly
- GM2 gangliosidosis
- Canavan syndrome
- MPS VI

Microcephaly
- Gaucher ds 2
- Nieman Pick ds
- PKU, Maternal PKU
- PDHC def.
- Fumarase def.
- Formiminotransferase def.

Hyperthermia
- Luft syndrome

Macroglossia
- Congenital hypothyroidism
- Pompe ds
- Fucosidosis
- Beckwith Wiedman syndrome
- Mitochondrial complex IV def.

Muscle atrophy
- ML I
- MLD
- GM2 gangiosidosis
- GSD III, GSD II-no muscle wasting

Muscle cramping or pain
- Muscle phosphoglycerate mutase def.
- GSD V, VII, X (GSD III-no pain)
- Fabry ds-xtremity pain
- Mitochondrial disorders

Nystagmus
- GSD III
- ML I, III
- MLD
- Leigh SNE
- Tyrosinemia II
- Pyruvate carboxylase def.
- Chediak Higashi syn
- Hermansky-Pudlak syn
- Waardenburg syn
- Cross syn

Photophobia
- Tyrosinemia II
- Cystinosis
- Chediak Higashi syn
- Hermansky-Pudlak syn
- Waardenburg syn
- Albinism

Platyspondyly
- MPS: IH, IS, IH/IS, II, III, IV

Refusal to feeding
- Organic acidemias
- Urea cycle disorders
- Lysinuric protein intolerance
- Nonketotic hyperglycinemia
- Galactosemia (UT def.)
- Hereditary fructose intolerance
- Krabbe ds

Proteinuria
- Fabry ds
- Wilson ds
- GSD I
- Galactosemia (UT def.)
- Hereditary fructose intolerance

Psychomotor retardation
- Oligosaccharidosis: Mannosidosis, Fucosidosis
- Mucolipidosis: ML II, ML IV
- Sphingolipidosis: NP ds, GM1, GM2, Krabbe, Canavan
- Peroxisomal disorders
- Mitochondrial disorders: Leigh SNE, PDHC

def., PC def.
- Fructose-1,6-diphosphatase def.

Pulmonary involvement
- Gaucher ds
- NP ds
- GSD II (aspiration pneumonia)

Ptosis
- Myasthenia gravis
- Mitochondrial myopathy

Psychosis, Emotional lability
- Wilson ds
- Hyperargininemia
- MLD
- Gaucher type 3
- Nieman Pick C
- ALD

Recurrent Infection
- GSD 1b
- GSD II (lung infection)
- Prolidase def.
- Mannosidosis
- Chediak Higashi syn

Renal failure
- Hyperoxaluria
- Cystinosis
- Fabry ds
- GSD V (d/t myoglobinuria)

Scoliosis
- MPS: IH, VI
- Aspartyl glucosaminuria
- Fucosidosis

Seizure
- Urea cycle disorders
- Organic acidemias: MMA, PA, IVA, Multiple carboxylase def., Prolinemia, B6 responsive sz, NKH
- Mitochondrial disorders: Complex I, Leigh SNE, PC def., PDHC def.,
- Galactosemia
- GSD: GSD 0, GSD 1, GSD III
- Lysosomal storage disorders: Sialidosis, Neuronal ceroid ipofuscinosis, MLD, Krabbe, Alpers, Gaucher 3, GM2, ML I
- Homocystinuria I, III
- Sulfite oxidase def.
- BH4 deficiency
- Formiminotransferase def.

Vomiting
- Urea cycle disorders
- Organic acidemias: PA, 3-HMG aciduria, ketolytic defect, IVA, MSUD, Holocarboxylase synthetase def., Pyroglutamic acidemia
- Galactosemia (UT def.)
- Tyrosinemia[15, 16)]
- PKU
- Hereditary fructose intolerance
- Leigh syn
- Wolman ds

Weakness
- Mitochondrial disorders: Leigh SNE, Complex I, III. IV def.
- Sphingolipodosis: GM1, Fabry, MLD
- GSD: GSD II, III, X
- Refsum ds
- Carnitine def.

After symptomatological evaluation, routine

basic laboratory tests such as CBC, U/A, LFT, Ammonia, Gas analysis, Lactate/Pyruvate can give you very important clue also. Initial sample is very important. The organic acid pattern of mild form normalizes rapidly after infusion of IV glucose and that coul be major source of misdiagnosis. So if there's any possibility of IEM, Store urine sample for organic acid analysis and aminoacid analysis in refriegerator or freezer before IV glucose infusion.

Metabolic acidosis
- Organic acidemias: all
- GSD I, III (RTA)
- Galactosemia (UT def.)
- Carnitine def.
- Mitochondrial disorders: PDHC def., PC def.

Hyperammonemia
- Urea cycle disorders: Severe. CPS, OTC, AS, AL, Arginase, NAGS, Lysinuric protein intolerance, HHH syndrome
- Organic acidemias: Moderate
- Fatty acid oxidation disorders: MCAD def.
- Reye syndrome
- Ketolytic defects
- Transient hyperammonemia of newborn

Hyperketosis, Ketonuria
- Organic acidemias
- GSD I, 0
- Ketolytic defects
- Fructose -1,6-diphosphatase def.
- Pyruvate carboxylase def.

Hyperuricemia
- Gout
- Lesch-Nyhan syn
- GSD I
- Hyperoxaluria I, II
- Hereditary fructose intolerance
- Hereditary fructose-1,6-diphosphatase def.
- Tumor lysis syn
- DKA
- Down syn

Hypoglycemia
- GSD: 0, I, III, VIII
- Galactosemia: UT def.
- Hereditary fructose-1,6-diphosphatase def
- Herediary fructose intolerance
- Mitochondrial disorders: PDHC def., PC def. OXPHOS def.
- Fatty acid oxidation disorders: Carnitine def.
- Organic acidemias: PA, MSUD
- Tyrosinemia I

Lactic acidosis
- Mitochondrial disorders: PDHC def., PC def., Respiratory chain disorders,
- GSD 0, I
- FAOD: Carnitine d.ef
- Alpers syn

Liver dysfunction
- Tyrosinemia
- Galactosemia
- Wilson ds
- Gaucher ds
- GSD IV, VI, IX, XI
- Alpers syn
- Zellweger syn
- HMG aciduria
- Hereditary fructose intolerance

Neutropenia
- GSD Ib
- Chediak Higashi syn
- Lysinuris protein intolerance
- Organic acidemias: MMA, PA, IVA

Thrombocytopenia
- Gaucher ds
- Organic acidemias: MMA, PA, IVA
- Hereditary fructose intolerance
- Chediak Higashi syn

Foamy Histiocyte in BM
- Nieman Pick ds
- Gaucher ds
- GM1 gangliosidosis type I
- Fucosidosis
- Fabry ds
- Wolman ds

After clinical approaches are done, biochemical screening tests such as organic acid analysis of urine, aminoacid analysis of plasma, Tandem MS analysis of DBS, including GL-3, acylcarnitine profiles for FAOD, and urine GAG can give you much more precise informations. These tests except urine GAG are also biochemical confirmatory tests. Enzyme assay is final biochemical confirmatory test, if feasible. But it's not so easy to do enzyme assay because of rareness. Pathologic diagnosis with peripheral blood smear, BM, liver or L/N can give you important clues for diagnosis of lysosomal storage disorders and glycogen storage diseases but no specific findings of organic acidopathies, aminoacidopathies and urea cycle disorders. That's the reason why autopsy can not give any informations about these disorders.

Molecular Studies such as CGH, PCR and nowadays NGS can give you confirmatory results.

Conclusion

IEMs are very complex and embarassing disease groups but if meticulous history taking and basal laboratory tests can categorize and summarize them into relatively small differential diagnosis lists and make systemic diagnostic approach possible.

한 글 요 약

유전성대사장애질환의 진단과 치료는 최근들어 비약적인 발전을 하고 있으며, 치료가 불가능하여 대증적인 치료만이 가능하였던 많은 병들이 치료가 가능하여지고 있다. 이러한 사실은 비가역적인 후유증이 생기기전의 조기진단의 중요성을 더 크게 한다. 유전성대사장애질환은 현재 밝혀진 것만 하더라도 수백 가지의 질병에 이르며, 가까운 미래에 그 수는 수천에 이를 것으로 전망되고 있다. 이와 같은 질병의 다양성과 그 증상 및 임상적발현의 다양성은 임상의들이 정확한 진단에 이르는데 크나큰 장애요인이 되고 있다. 신생아기와 영아기 초기의 임상적인 발현은 비특이적이지만 나이가 들어가면서 다양한 특징적인 증상을 나타내게 된다. 같은 질병일지라도 잔류효소농도(residual enzyme activity)가 거의 없는 경우에는 신생아기 또는 영아기 등 이른시기에 증상이 나타나지만 잔류효소농도가 어느 정도 남아 있는 경우에는 늦게 소아기 또는 성인기에 증상을 나타내며, 유기산이나 지방산대사이상의 경우에는 이화작용이 증가되는 스트레스상태에서 갑작스런 악화를 보일 수도 있다. 본 논문에서는 이러한 다양한 증상과 검사소견들을 정리하여 보고, 그러한 증상을 일으키는 주된 질병들을 정리하여 감별진단과 검사를 체계적으로 접근할 수 있도록 하였다.

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