Atlas of Neurometabolic Disorders

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By

Parvaneh Karimzadeh

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PREFACE

Neurological manifestations are the prominent signs and symptoms of neurometabolic diseases, an important group of hereditary disorders. Global neurodevelopmental delay is the first symptom in many patients. Seizure is also a common neurological sign, which is often refractory to anti-seizure medications if the underlying disease is not treated. Neurometabolic disorders mostly present in newborns and infants with severe clinical manifestations, including poor feeding, vomiting, lethargy, seizures, and loss of consciousness during metabolic decompensation. Although these presentations are often fatal, severe neurological insult and regression of neurodevelopmental milestones are prominent signs in surviving patients. Therefore, it is important to treat the acute symptoms immediately, regardless of the cause. In the late infantile period and childhood, symptoms of neurometabolic disorders normally develop after an interval of normal or near normal growth and development. These children, without early diagnosis and treatment, may experience recurrent episodes of vomiting, lethargy, and loss of consciousness due to environmental stresses, such as upper respiratory tract infection, vaccination, and surgery. Also, children may show regression in motor and mental skills after one or two years. A number of patients with neurometabolic disease respond remarkably well to appropriate treatment. Therefore, early detection and intervention can be invaluable in some cases to prevent catabolism and to promote normal or near normal neurodevelopmental milestones.

Authored by a pediatric neurologist, this atlas discusses different neurometabolic disorders and presents an introduction to their clinical and neurological manifestations, case presentations, imaging findings, laboratory studies, neuroimaging results, and electroencephalography (EEG) data.

Pediatric neurologists, pediatric endocrinologists, medical interns, and medical students can find common neurometabolic disorders, along with case presentations and imaging findings in different chapters of this book.

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CHAPTER 1

AMINOACIDOPATHIES

1.1. Maple Syrup Urine Disease (MSUD)

Introduction

Maple Syrup Urine Disease (MSUD) is an autosomal recessive metabolic disorder, caused by branched-chain α-ketoacid dehydrogenase (BCKAD) complex deficiency. This disorder is associated with an increase in the level of branched-chain amino acids (BCAAs), including urine α-ketoacidosis and plasma valine, leucine, and isoleucine (1). Classic or neonatal MSUD is characterized by failure to thrive, lethargy, irritability, refractory vomiting, weak muscle tone (hypotonia), and a maple syrup odor of the body, especially in the cerumen and urine. Progression of this disease without treatment can cause neurological manifestations, such as spasticity, opisthotonus, dystonia, and seizures (2). Neuroimaging findings indicate mild to moderate brain atrophy and delayed myelination associated with brain edema in the acute form of the disease (3). Diagnosis, which is based on a marked increase in the plasma level of BCAAs, is confirmed using enzymatic and genetic assays (4).

Case Presentation

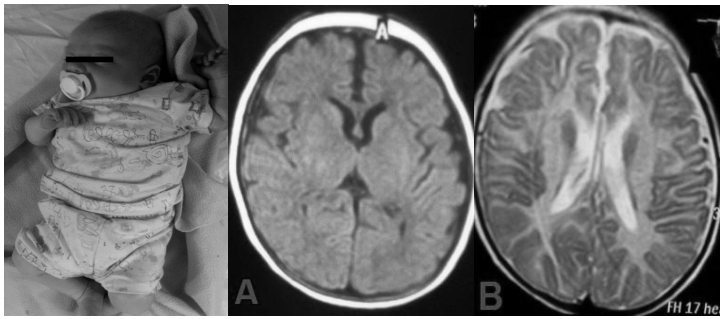

Figure 1-1: A four-month-old girl with MSUD, who was referred to our neurometabolic clinic due to hypotonia, irritability, spasticity, and seizures. Axial FLAIR MRI shows mild generalized cerebral atrophy (A). Axial T2W MRI indicates the same finding, as well as delayed myelination with white matter (WM) edema (B).

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1.2. Phenylketonuria (PKU)

Introduction

Children with Phenylketonuria (PKU) appear normal at birth and have normal neurodevelopmental milestones in early infancy, whereas their head circumference and developmental delay gradually decrease. These children may have a musty odor, especially in the urine due to metabolites of phenyllactic acid and phenylpyruvic acid. Behavioral disorders and autistic spectrum disorders are common in these children. Also, MRI findings show the high intensity of periventricular WM (dysmyelination); however, these findings are reversible with a restricted phenylalanine diet.

The severity of MRI findings (WM involvement) is correlated with the mean phenylalanine level in previous years and at the time of brain imaging. Many studies have reported a significant correlation between the serum phenylalanine level and WM involvement on MRI, based on conventional methods. These studies have reported the higher sensitivity of diffusion-weighted imaging (DWI). In this regard, Karimzadeh et al., in a study on MRI changes in 30 patients with PKU, showed that measurement of the mean phenylalanine level for one year is the best indicator of WM involvement. This indicator had a more significant relationship with MRI findings, compared to phenylalanine level at the time of imaging. Magnetic resonance spectroscopy (MRS) of PKU patients indicates a phenylalanine peak at 7.37 ppm. Generally, the peak size is useful for monitoring the serum phenylalanine level and treatment. In addition, abnormal EEG findings, including generalized paroxysmal activity and generalized slowing, are common even in well-treated patients.

Case Presentation

A 14-year-old boy was referred to our neurometabolic clinic due to autistic spectrum disorder, mental disability, and seizures. The patient had a history of neurodevelopmental delay. He was able to walk only at age four and talk at age six. First, he showed behavioral disorders, such as autistic spectrum disorder. He had a history of two seizure attacks, controlled by anti-seizure medications. He also had a history of eczema and skin rash on his face. MRI findings showed abnormal signal changes in WM. Tandem mass spectrometry was carried out. Amino acid analysis showed a significant increase in the level of phenylalanine (715.1 μmol/L or 11.8 mg/dL). It should be noted that the patient was born before the establishment of the Newborn Screening Program for PKU in Iranian newborns.

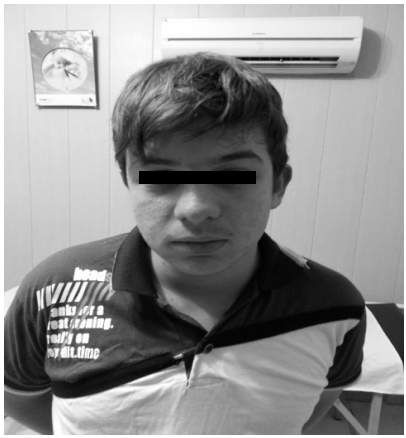

Figure 1-2: The patient's image with a light hair color (atypical in Iranians) and skin tags

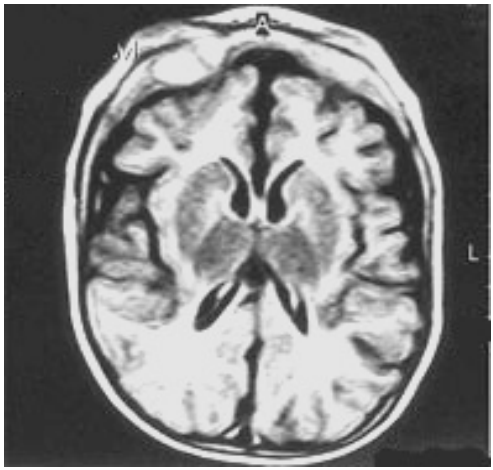

Figure 1-3: Abnormally high signal intensity in WM region around the anterior and posterior horns of both lateral ventricles and cerebral atrophy

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1.3. Non-Ketotic Hyperglycinemia (NKH) or Glycine Encephalopathy

Introduction

NKH is usually classified into two main clinical types: neonatal and late-onset. The neonatal type of NKH is recognized as the most common. This disease is transmitted as an autosomal recessive trait (1). Although patients with NKH appear normal at birth, they develop progressive encephalopathy, characterized by lethargy, axial hypotonia, and decreased Moro reflex within the first few hours and after feeding. In these patients, respiration becomes increasingly irregular, culminating in apneic attacks, which result in a deep coma, myoclonus, and eventually tonic or clonic seizures. Hiccups are also often present in these patients (2).

According to EEG findings, NKH is characterized by burst suppression. The bursts are mostly asynchronous in both hemispheres and comprise irregular slow waves, sharp waves, and spikes (2). MRI shows progressive cortical atrophy, callosal thinning, and delayed myelination in NKH. Also, neonatal hypotonia may gradually evolve into spasticity. Most patients die before the age of five. When NKH is suspected clinically, plasma amino acids should be analyzed. Diagnosis of NKH is based on either an increase in the absolute value of glycine in the cerebrospinal fluid (CSF) or an increase in the CSF-to-plasma glycine ratio. The mean ratio was measured to be 0.11 to 0.17±0.09 in different studies, whereas in the controls, the corresponding ratio was <0.02 (3).

Case Presentation

A nine-month old infant was referred to our neurometabolic department due to seizures. The type of seizure was epileptic spasm, which had initiated at the age of three months and was refractory to appropriate anti-seizure medications. He had a history of hiccups and frequent myoclonic jerks in the neonatal period. Neurological examination showed global neurodevelopmental delay, mild to moderate hypotonia, microcephaly, exaggerated deep tendon reflexes (DTRs), and visual impairment.

MRI was carried out for the patient, which indicated high signal intensity in the posterior limbs of internal capsules, suggesting abnormal myelination. EEG also revealed a diffuse burst suppression pattern. Neurometabolic evaluation indicated the high serum level of lactate, normal ammonia, normal venous blood gas, and an elevated glycine level

on high-performance liquid chromatography (HPLC) of plasma and urine. Moreover, the CSF glycine level increased, similar to the CSF-to-plasma glycine ratio (>0.08).

Treatment was initiated using sodium benzoate to reduce the serum glycine level. Benzoate binds to glycine to form hippurate, which is excreted in the urine. This treatment could reduce seizures and improve alertness. We closely monitored the plasma glycine level to ensure that sodium benzoate was at an effective and non-toxic level. Also, dextromethorphan was used to reduce seizures and improve cognition and alertness. Generally, dextromethorphan binds to NMDA receptors in the brain, preventing glutamate from receptor binding. It is known that dextromethorphan, together with benzoate, can improve attention and developmental milestones, and lower the frequency of seizures.Seizure management in patients with severe classic NKH is difficult and usually requires multiple anticonvulsants. Glycine can act as a co-agonist at the excitotoxic glutamate NMDA receptor site. It is hypothesized that the excess glycine saturates the NMDA co-agonist binding site, causing excessive excitatory neurotransmission and postsynaptic toxicity. Therefore, administration of valproic acid must be avoided as it inhibits the hepatic glycine cleavage system.

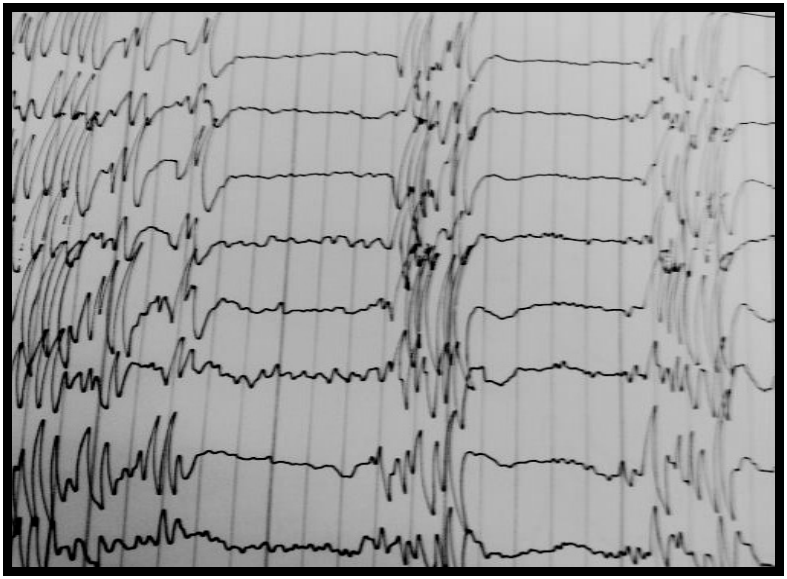

Figure 1-4: Burst suppression pattern on EEG

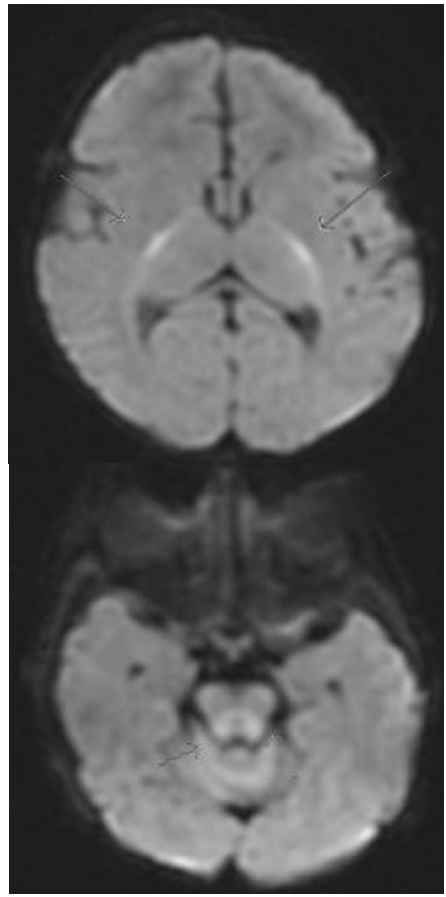

Figure 1-5: Brain MRI indicates the symmetric high signal intensity in the posterior limbs of internal capsules, suggestive of abnormal myelination.

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1.4. Isolated Sulfite Oxidase Deficiency (ISOD)

Introduction

Isolated Sulfite Oxidase Deficiency (ISOD) is a rare metabolic disorder and an enzyme deficiency, which is inherited with an autosomal recessive pattern. Sulfite oxidase catalyzes the oxidation of the cysteine sulfur atom into inorganic sulfate. A deficiency of sulfite oxidase results in the accumulation of a suspected toxic compound, called sulfite, together with its detoxification products, S-sulfocysteine and thiosulfate. It is also associated with the reduced formation of sulfate (1). ISOD patients present with early refractory convulsions, severe psychomotor retardation, failure to thrive, and microcephaly (2).

Case Presentation

A 30-month-old boy was referred to our clinic with seizures and severe neurodevelopmental delay, without fix and follow of objects. The neurological examination showed microcephaly, dystonia, and spasticity. Also, his DTRs had increased. He was the child of consanguineous parents, without an eventful birth history. In all neurometabolic screening tests, urinary organic acid, lactate, and ammonia were within the normal limits. His first sibling had died due to similar findings. MRI was carried out, which revealed severe cerebral atrophy with cystic encephalomalacia. The level of sulfite increased in the fresh urine sample. Whole exome sequencing (WES) detected a homozygous variant in *SLOX* gene (c.1376G>A, p.R459Q). It should be noted that mutations in the *SLOX* gene can cause ISOD.

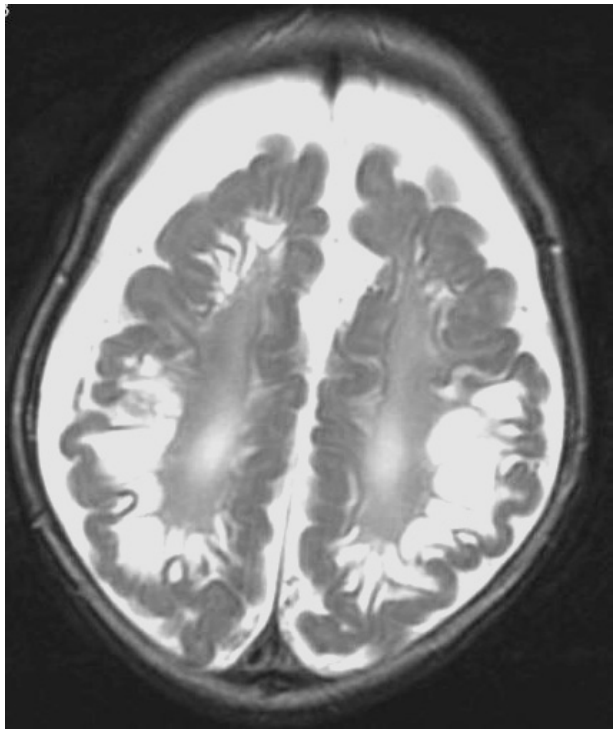

Figure 1-6: Severe brain atrophy and cystic encephalomalacia (especially in the posterior region).

Figure 1-7: Dystonia in the patient.

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CHAPTER 2

UREA CYCLE DISORDERS

2.1. Ornithine Transcarbamylase Deficiency

Introduction

In this chapter, six congenital urea cycle disorders are described. All these disorders are autosomal recessive, except ornithine transcarbamylase deficiency as an X-linked disorder (1). They are characterized by deficiencies in carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, arginase, and N-acetylglutamate synthase (2). They are also correlated with hyperammonemia and amino acid metabolism; however, no acidosis occurs in these disorders.

Presentation of these disorders in the neonatal period is typically overwhelming, as they rapidly progress from poor feeding, vomiting, lethargy, irritability, or tachypnea to convulsion, coma, and respiratory failure. In infancy, symptoms are less severe and more variable. Generally, poor developmental progress, behavioral problems, hepatomegaly, and gastrointestinal symptoms are common. Children and adults typically present with chronic neurological disorders, characterized by variable behavioral problems, confusion, irritability, and episodic vomiting (1). The most common presentation is ornithine transcarbamylase deficiency (2).

Case Presentation

A 14-month-old boy was referred to our neurometabolic clinic due to severe hyperammonemia. He was the child of consanguineous parents. He had severe hypotonia with no fix and follow in the visual assessment, in addition to refractory seizures since infancy. Neurometabolic evaluation showed an increased glutamine level on HPLC and severe hyperammonemia (320 Umol/L). Venous blood gas showed respiratory alkalosis, while other

neurometabolic indices, such as acylcarnitine profile and serum lactate, were within the normal limits. Evaluation of urinary organic acids showed the high level of orotic acid, while plasma amino acid evaluation indicated the low level of citrulline. He presented with two episodic hyperammonemia encephalopathies. Also, altered mental status and increased seizure frequency were reported following severe hyperammonemia, provoked by the febrile disease, fasting, and medications. The enzyme assay confirmed the diagnosis of ornithine transcarbamylase deficiency.

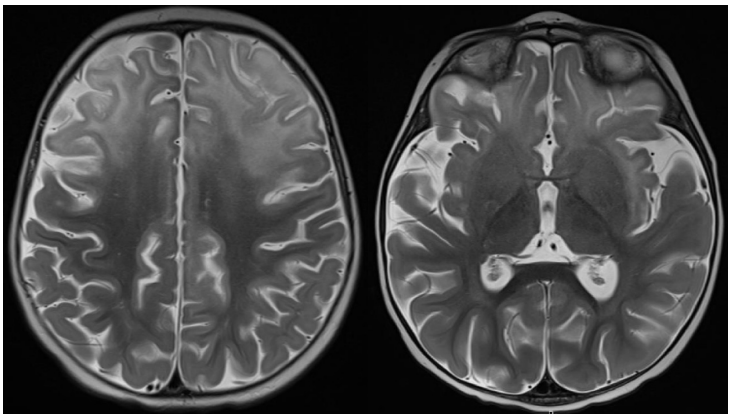

Figure 2-1: A 14-month-old boy with ornithine transcarbamylase deficiency and hyperammonemia.

Table 1: Levels of citrulline and orotic acid in plasma amino acids and urine organic acids in urea cycle disorders.

Disorders	Plasma Amino Acids	Urine Organic Acids
N-AcetylglutamateSynthetase Deficiency	Low Citrulline	Low Orotic Acid
Carbamoyl Phosphate Synthetase Deficiency	Low Citrulline	Low Orotic Acid
OrnitineTranscarbamylase Deficiency	Low Citrulline	High Orotic Acid
ArginosuccinateSynthetase Deficiency	High Citrulline	High Orotic Acid
ArginosuccinateLyase Deficiency	High Citrulline	High Orotic Acid, High Arginosuccinic acid
Arginase Deficiency	High Citrulline	High Orotic Acid

2.2. Argininosuccinic Aciduria

Introduction

Argininosuccinic aciduria is a rare neurometabolic disorder, characterized by lack or deficiency of argininosuccinate lyase (ASL). ASL is one of six enzymes, which play a role in the breakdown and removal of nitrogen from the blood; this process is known as the urea cycle. Five disorders, involving different defects in the biosynthesis of urea cycle enzymes, have been described, including ornithine transcarbamylase deficiency, carbamoyl phosphate synthetase deficiency, argininosuccinate synthetase deficiency or citrullinemia, ASL deficiency, and arginase deficiency. A lack of ASL can lead to the excessive accumulation of nitrogen in the form of ammonia in the blood (hyperammonemia).

Ammonia is a neurotoxin, which disrupts the function of neurons in the central nervous system. High levels of ammonia travel to the central nervous system through the blood, producing the neurological manifestations of argininosuccinic aciduria. Infants may experience vomiting, poor feeding, progressive lethargy, and finally, loss of consciousness. This disease is inherited as an autosomal recessive trait and is usually detectable in the first few days of life. Newborns with argininosuccinic aciduria may present with lethargy and poor feeding. Some infants may experience seizures or sudden jerks and twitching of the body.

Complications of argininosuccinic aciduria include developmental delay and intellectual disability in some patients. Progressive skin lesions and brittle hair may be also reported. Some individuals may inherit a milder form of this disorder, where ammonia only accumulates in the blood during periods of illness, fever, and other stresses. These patients may have near normal development, whereas infectious diseases or stress can result in lethargy and loss of consciousness.

Case Presentation

A six-year-old boy was referred to our neurometabolic center due to loss of consciousness. Because of the low level of consciousness, he was admitted to the pediatric intensive care unit (PICU) for two months, followed by two weeks in the pediatric neurology ward. He was the child of consanguineous parents with an uneventful birth history. He had a normal motor development, despite speech delay. Moreover, he had a

history of kinky and sparse hair, besides skin dermatitis. One attack of generalized tonic-clonic seizure was reported, which was controlled by anti-seizure medications.

Meningoencephalitis was the first diagnosis. Lumbar puncture was carried out to evaluate all bacterial and viral causes of meningoencephalitis. Normal glucose and protein levels were reported, and no white blood cells or red blood cells were detected; also, all infectious agents were negative. Brain MRI was in the normal limit; therefore, other causes, such as acute demyelinating encephalomyelitis and space-occupying lesions, were ruled out. EEG showed some slowing patterns.

The patient's serum lactate level and venous blood gas were not significant. Minimally elevated ammonia was reported in the patient. The results of routine biochemical laboratory tests were normal. Metabolic screening tests (tandem mass spectrometry-MS/MS) indicated a high level of citrulline (76.1 µmol/L; NL< 60). The level of argininosuccinic acid was 16.7 µmol/L (NL<1.5). He was diagnosed with argininosuccinic aciduria. Treatment was initiated using sodium benzoate, arginine, and a special diet and formula for argininosuccinic aciduria. He responded remarkably well to this treatment.

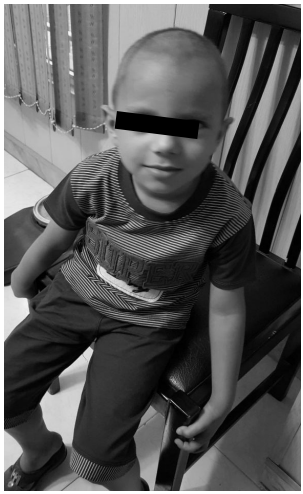

Figure 2-2: Kinky and sparse hair of the patient.

Figure 2-3: Effect of treatment after nine months.

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