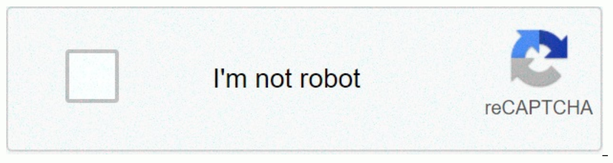

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Amino acid metabolic disorders pdf

13422-51-0 22465-48-1 78091-12-0 8017-22-9 a-(5,6-Dimethylbenzimidazolyl)hydroxocobamide Acti-B12 alpha Cobione alpha-(5,6-Dimethylbenzimidazolyl)hydroxocobamide AlphaRedisol AlphaRedisol (TN) Axion Axlon Benzimidazolyl ribofuranosyl phosphate deriv. C08230 C62H85CoN13O15P CHEBI:27786 CHEMBL1200742 CHEMBL235822 CID11622291 CID11953898 CID5460373 CID6433575 CID6474319 Ciplamin H Coalpha-[alpha-(5,6-dimethylbenzimidazolyl)]-Cobeta-hydroxocobamide Cobalex Cobalin H Cobinamide dihydroxide dihydrogen phosphate (ester), mono(inner salt), 3'-ester with 5,6-dimethyl-1-alpha-D-ribofuranosylbenzimidazole Cobinamide hydroxide phosphate 3'-ester with 5,6-dimethyl-1-a-D-ribofuranosylbenzimidazole inner salt Cobinamide hydroxide phosphate 3'-ester with 5,6-dimethyl-1-alpha-delta-ribofuranosylbenzimidazole inner salt Cobinamide hydroxide phosphate 3'-ester with 5,6-dimethyl-1-alpha-D-ribofuranosylbenzimidazole inner salt Cobinamide, Co-hydroxy-, dihydrogen phosphate (ester), inner salt, 3'-ester with (5,6-dimethyl-1-alpha-D-ribofuranosyl-1H-benzimidazole-kappaN3) Cobinamide, Co-hydroxy-, f-(dihydrogen phosphate), inner salt, 3'-ester with (5,6-dimethyl-1-alpha-D-ribofuranosyl-1H-benzimidazole-kappaN3) Cobinamide, dihydroxide, dihydrogen phosphate (ester), mono (inner salt), 3'- ester with 5,6-dimethyl-1-alpha-D-ribofuranosylbenzimidazole Cobinamide, dihydroxide , dihydrogen phosphate (esters), mono (salt inside), 3'-ester with 5,6-dimethyl-1-alpha-D-ribofuranosyl-1H-benzimidazole Cobinamide, hydroxide, dihydrogen phosphate (ester), salt inside, 3'-ester with 5,6-dimethyl-1-alpha-D-ribofuranosyl-1H-benzimidazole Codroxomin Cyanokit Cyanokit (TN) D01027 DB00200 Depogamma Docclan Docelan Docelvita Docevita Droxomin Ducobee hy Ducobee-Hy Duradoce Duralta-12 EINECS 236-533-2 Hidroxocobalamina Hidroxocobalamlamina [INN-Spanish] HSDB 3342 Hydro Cobex Open access peer-reviewed chapterBy Yana SandlersSubmitted: November 16, 2018Reviewed: January 23rd 2019Published: March 8th 2nd 019DOI: 019DOI 10.5772/intechopen.84672 Congenital metabolic error (IEM) represents a group of genetic diseases in which genetic defects lead to blocks on a metabolic path, leading to a single enzyme dysfunction. As a downstream consequence of the remaining or complete loss of enzyme activity, there is an accumulation of toxic metabolic substances near the metabolic mass and/or deficiency of an essential metabolic product that leads to the clinical manifestation of the disease. While individual IEMs are rare, the overall estimated incidence of metabolic genetic disorders is 1:800. The genetic basis of IEMs may be related to anotypes such as point mutations, deletion or insertion, or more complex genome rearraons. IEM classification can be done simply on the basis of the affected metabolic network: fatty acid oxidation disorders, protein/amino acid metabolism disorders, carbohydrate metabolism disorders, lysosomal storage diseases, peroxisomal disorders and Sick. This chapter will overview genetic disorders related to amino acid metabolism and amino acid analysis for regular diagnosis and monitoring of this faulty IEMs.inborn type of acid metabolismamino disorder analysis of acidAmino mass cym identity exchange (Figure 1) plays many important roles in our body: they are basal structural protein units and prefigured substances of neuro-transmission, porphyrins and nitric oxide. Furthermore, amino acids derived from dietary proteins serve as energy sources since while catabolized in our body, amino acids that form organic acids can supplement Krebs cycles and ammonia that eliminate through the urea cycle.[1]. The general structure of amino acids consists of an amino group, a carboxylic group and a variable R lateral chain that has a great influence on soothipity and polarity. Amino acid disorders (also known as aminoacidopathies) are a group of congenital errors of metabolic diseases, caused by genetic defects in the path involved in amino acid metabolism. All major amino acid disorders (Table 1) under a self-diving mode of inheritance mean that mutations cause a metabolic mass to be present in the genetic material of both parents. As a result of mutations, genetic defects are reflected downstream as a deficiency or a biological activity part of the enzymes involved in amino acid metabolism. Therefore, some substrates in these paths accumulate or are redirected into alternative paths. Therefore, amino acid disorders are characterized bio-biosyn chemically by abnormal levels of single or certain amino acids and their downstream plasma and/or urine metabolism (Table 2–6). Amino acid disorders are presented with altered and often nonsom specific clinical symptoms. In combination with medical assistance, these disorders are managed by nutritional restrictions, supplements and medical foods that limit the consumption of a violating amino acid or in some cases protein consumption. Therefore, it is important to regularly perform amino acid analysis to monitor the results of dietary treatment in people who have been diagnosed. In the following chapters, the main amino acid disorder is considered and analysis of dosing amino acids in clinical settings is discussed. Aromatic amino acid disorderDisorder nameAmino acid involvedEnzyme or transport defectAdditional biomarkersPKU classicalPhe (B) highPAHPhe: Tyr ratio (B), phenylpyruvic, phenyllactic and 2-hydroxyphenylacetic acid (U)Defects of biopterin cofactor biosynthesisPhe (B) highGTPCHLow biopterin, neopterin (U)Defects of biopterin cofactor biosynthesisPhe (B) highPTPSLow biopterin, high neopterin (U)Defect of cogeneration factor biopterinPhe (B) highPCBD1High neopterin and primapterin (U)Defect of copper regeneration weak biopterinPhe (B) highDHPRHigh biopterin (U) and low DHPR activity in dry blood spotsTyrosinemia ITyr (B) highFAHSuccinylacetone (DBS, U), 4-hydroxy-phenylpyruvic, IITyr (B) highTAT4-hydroxyphenylpyruvic, 4-hydroxy-phenyllactic acid (U)Tyrosinemia IIITyr (B) highHPPD4-hydroxyphenylpyruvic, 4-hydroxyphenyllactic acids (U)Laboratory findings in aromatic amino acids disorders. PAH, nmol hydroxylase; GTPCH, GTP cyclohydrolase; PTPS, 6-pyrovoyltetrahydropterin synthase; PCBD1, pterin-4a-carbinolamine dehydratase; DHPR, dihydropterin reductase; FAH, fumarylacetoacetate hydrolase; TAT, tyrosine aminotransferase; HPPD, 4-hydroxyphenylpyruvate dioxygenase. AminDisorder acid chain branching disorder NameAmino acid involvedEnzyme or transport defectAdditional biomarkersMSUDBCAA (B) high, allo-Ile (B) highBCKDCPlasma ratio of Val:Ile:Leu (3.5:1:2), branch chain 2-ketoacids and 2-hydroxyacids (U)Laboratory findings in MSUD. BCKDC, branching chain ketoacid dehydrogenase complex. UreaDisorder nameAmino acid cycle disorder involvedEnzyme or transport defectAdditional biomarkersCitrullinimia ICit (B) markedly elevatedASSHyperammonemia, orotic acid (U), may be accompanied by high glutamine and alanine (B)Citrullinimia II/citrin deficiencyCit (B) moderately high, Met, Lys (B) Asp/Glu mitochondrial exchangerHyperammonemia, orotic acid (U). Citrulline is moderately elevatedCPS-I deficiencyCit (B) lowCPS1Can be accompanied by high glutamine and alanine (B) Ornithine transcarbamylase deficiencyCit (B) lowOTCNonspecific amino acid profile: increased glutamine, alanine and decreased ornithine, arginine (B). Axit orotic (U) tăng rõ rệtArginino-succinic acidemiaASA (B), (U) elevatedASLLow citrulline, thấp arginine (B)ArgininemiaArg (B) highArginaseOrotic acid (U), Bình thường hoặc giảm citrulline (B)HHHOrn (B, U), highORC1Homocitrulline (U) highCo-factor sản xuất N-axetyl glutamate synthetase deficiencyGln (B) highNAGSCit (B) thấp, alanine cao (B) Phát hiện trong phòng thí nghiệm trong chu kỳ urê Rối loạn axit amin lưu huỳnhDisorder nameAmino acid involvedEnzyme or transport defectAdditional biomarkersHomocystenuriaFree homocystine (B, U) highCBSTotal Hcy và methionine (B, U)S-Adenosyl-homocysteine-hydroxylase deficiencyMet (B) highAdoHcyasMildly elevated total plasma Hcy, S-adenosylhomocysteine, (B), S-adenosylmethionine (B)Sulfate oxydase deficiencySSC* (B, U) highSUOXTaurine, U) Thiếu hụt cofactor MolypdenSSC* (B, U) highSUOX, XDH, AOTaurine, cystine thấp (B, U), hypoxanthine và xanthine tăng cao (U), axit uric thấp (B)Glycine-N-methyltransferase deficiencyMet (B) highGNMTS-adenosylmethionine (B)Hyper-methioninemiaMet (B) highMATLaboratory phát hiện trong rối loạn của axit amin lưu huỳnh.*S-sulphocysteine có thể không được phát hiện trong huyết tương bằng cách sử dụng phương pháp thường xuyên trong sulfite oxidase và molypden co-factor deficiency. CBS, cystathionine beta synthase; AdoHcyas, S-adenosylhomocysteine hydroxylase; SUOX, sulfate oxidase; XDH, xanthine dehydrogenase; AO, aldehyde oxidase; GNMT, glycine-N-methyltransferase.Disorders of amino acids transportDisorder nameAmino acid involvedEnzyme/transport defectAdditional GNMT, of amino acids transportDisorder nameAmino acid involvedEnzyme/transport defectAdditional GNMT, glycine-N-methyltransferase.Disorders of amino acid transportDisorder nameAmino acid involvedEnzyme/transport defectAdditional GNM GNM (U) increaseCystine and dibasic amino acids in the gastrointestinal tract and renal t dibassine, ornithine, increased arginine (U)Lysinuric protein intolerance (U) significantly increases the transport amincationic acid SLC7A7Arginine, moderately increased ornithine (U), orotic acid syndrome (U)Fanconi All amino acids increase (U)Defects in the vitro nearThe detection in kidney aminoacidurias. GlycineDisorder metabolic disorder nameAmino acid involvedEnzyme/transport defectAdditional biomarkersNonketotic hyperglycemia (NKH)Gly (B, CSF) highMutations in Gly cleavage systemIncreased CSF/plasma Gly ratioSlaboratory findings in NKH. B, blood; CSD, cyel fluid. Phenylketonuria (commonly known as PKU, a ratio of 1 in 13,500 to 19,000 born in the United States[2]) is a genetic disorder of phenylalanine metabolism characterized by a deficiency of phenylalanine hydroxylase (Figure 1). The enzyme catalyst converts phenylalanine into tyrosine in the presence of tetrahydrobiopterin (BH4) as a cofactor. Based on plasma phenylalanine concentrations, PKU is classified as severe pheno pheno pheno pheno pheno pheno phenost (Phe > 1200 µmol/L), mild (Phe = 600–1200 µmol/L) and hyperphenylalaninemia (above normal cutting level but below 600 µmol/L). Clinical PKU can be presented with growth failures, global developmental delays, severe intellectual disabilities and other serious symptoms. During pregnancy, high levels of nmol have a monster effect on the developing fetus[3] and this condition is recognized as the mother's PKU. The accumulation of phenylalanine is also seen in defects of biosynming and biopterin cofactor regeneration[4] (Table 1). PKU's nutritional management aims to accumulate too much nmol by limiting the amount of natural proteins associated with the use of protein substitutes without nmol. The Tyrosine metabolic path consists of five enzyme reactions that take place mainly in liver cells and tubes near the kidneys. Tyrosinemia I am the most severe genetic disorder of tyrosine metabolism caused by a deficiency of fumarylacetoacetate hydrolase, the last enzyme in the catabolic tyrosine path. This disorder has a high incidence among french Canadians[5] and is associated with liver dysfunction. Tyrosinemia II is caused by a deficiency of aminotransferase tyrosine liver and manifested by mental retardation and other serious symptoms[6]. An active deficiency of 4-hydroxyphenylpyruvate dioxygenase leads to tyrosinemia III, a rare disorder characterized by mild mental retardation and/or seizures[7,8]. All three bioposyntic disorders characterized by high levels of plasma tyrosine (hypertyrosinemia) and urine excretion of downstream tyrosine metabolism agents (Table 1). Increased plasma tyrosine can also be seen due to transient tyrosinemia response to vitamin C in the newborn period (Figure 2). Reaction catalyst by phenylalanine hydroxylase. Tetrahydrobiopterin (BH4) is a co-factor of PAH. DHPR, dihydropteridine reductase; PCBD1, dehydratase. Maple syrup urine disease is a branch chain amino acid metabolic disorder caused by a complex deficiency of α acid dehydrogenase branching. MSUD is presented with five clinical stylings on the basis of age of onset, severity of symptoms, and response to thiamine supplementation[9]. MSUD is biosyn chemicals characterized by high plasma branching chain amino acids (leucine, isoleucine, valine, allo-isoleucine) and their abnormal proportions (normal ratio is valine:isoleucine:leucine/3.5:1:2). The disease is administered by a restricted leucine diet, due to which all branch chain amino acids and allo-isoleucine are regularly monitored. Classic MSUD is the most severe form of the disease characterized by no or very low remaining enzyme activity and clinical manifestations by developmental and neurological delays, brain disease, feeding problems and the characteristic smell of maple syrup in the urine. During protein metabolism, the carbon skeleton of amino acids is converted into gluconeogenic and/or ketogenic deposits while the nitrogen group is converted into ammonia through degradition. Toxic ammonia derived from amino acids and other metabolic sources is entering the urea cycle and is further converted into urea that is easy to excrete and non-toxic. Cycles that take place in the liver and deficiency of any enzymes or transport involved in the urea cycle can cause accumulation of ammonia (hyperammonemia) that has a highly toxic effect on the central nervous system. The overall estimated incidence of urea cycle disorders is 1:8000. All urea cycle disorders have inherited auto-diving, with the exception of ornithine-transcarbamylase deficiency (OTCD), which is associated with plasma X. Citrulline is an important amino acid in bio bioalytic diagnosis of urea cycle defects (Table 3). Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHH) is caused by mutations in the SLC25A15 or ORNT1 gene that lead to lack of translocase ornithine. Proteins transport ornithine, lysine, and arginine through the inner mitochondrial membrane in peripheral tissues and pericentral liver cells. ORC1 deficiency reduces the availability of mitochondrial ornithine, which leads to an increase in ornithine in cytosol (hyperornithinemia). In the liver, since mitochondrial ornithine is a necessary substrate for ornithine transcarbamylase (OTC), decreased levels of mitochondrial ornithine slow through the urea cycle (Figure 3). As a result of a decrease in the capacity of the urea cycle, the concentration of ammonia and carbamoyl-phosphate increases (increased blood mmonmony). At the same time, excess carbamoyl-phosphate is diverted to react with lysine to form homocitrulline (homocitrullinuria) or enter the pyrimidine path, to form orotic acid which is then excreted in the urine. Similarly, for other urea cycle disorders, early diagnosis in newborns may improve the clinical outcome of HHH. Urea cycle. ARG, arginase; ASS, argininosuccinate ASL, argininosuccinate lyase; CPS1, carbamoylphosphate I synthase; ORNT 1, mitochondrial ornithine transport; OTC, ornithine transcarbamylase. Homocystinuria is a methionine metabolic disorder (Figure 4). The main bio bio biomeductively detected in homocystinuria is the accumulation of an amino acid homocysteine containing sulfur and its metabolism in the blood and urine. Homocysteine is formed from methionine through transmethylation. Once created homocysteine can be irreversibly decomposed through the transsulfuration path to cysteine or remethylated back to methionine by methionine synthase. Remethylation involves transferring the methyl group from 5-methyltetrahydrofolate to homocysteine through cobalamin (Cbl) dependent methionine synthase (MT) and folate cycle link and homocysteine path. Homocysteine can also be remethylized through an additional path involving liver and kidney betaine-homocysteine methyltransferase. Defects in any of these steps can lead to homocystinuria. The classic homocystinuria is caused by cystathionine β-synthase deficiency (CBS)[10], an important enzyme in the trans-sulfur path that converts homocysteine into cystathionine. A block at cystathionine β-synthase limits transsulfuration to cysteine and results in both increased homocysteine and methionine, later caused by enhanced remethylation. Homocystinuria remethylation disorders include methylenetetrahydrofolate reductase deficiency (MTHFR) and defects of cobalamin metabolism (Cbl). It should be noted that methionine and non-homocysteine are analyzed through newborn screening, so MTHFR disorders and cobalamin defects may not be detected because methionine levels in these disorders may be normal. To increase detection rates in cobalamin-related disorders and MTHFR, several studies report the benefits of adding total homocysteine analysis to the diagnostic process[12]. Total homocysteine is

defined as the totality of all homocysteine species in plasma/serum, including free and protein-linked forms. The measurement of total homocysteine requires immediate separation and freezing of collected plasma. Sulfur amino acid conversion. CBS, cystathionine β synthase; Cbl, cobalamin; SAM, S-adenosyl methionine; SAH, S-adenosylhomocysteine; MAT, methionine adenosyltransferase; MS, methionine synthase; MTHFR, methylene tetrahydrofolate reductase; THF, tetrahydrofolate. Non-critical hypertension (NKH) is a serious disorder of glycine metabolic processes. Glycine is catabolized through a four-peptide separation complex. P-protein, a protein containing pyridoxal phosphate, T-protein, a protein necessary for tetrahydrofolate-dependent reactions, H-protein, a protein that carries intermediate aminomethyl and then hydrogen through false lipoyl multiples, and L-protein, a lipoamide dehydrogenase. This disorder is so severe, that most affected individuals die within a few of life or existence with significant intellectual disabilities. Key laboratory findings NKH is plasma glycine and CSF. Kidney aminoacidurias are disorders with genetic defects that affect the resaspiration of the renal tube. Therefore, these disorders are characterized by abnormal urinary amino acids. Early diagnosis can prevent the serious effects of congenital metabolic errors, including amino acid disorders and significantly reduce the incidence and mortality. Newborn screening is a public health program where facilities diagnose early by identifying infants with potential faults for congenital treatment of metabolism at an early stage of their lives. This practice helps to manage the disease even for infants with no obvious symptoms in the first days of life. Amino acid analysis has always been an important part of newborn screening. The first PKU screening bacteria inhibitor test was invented by Robert Guthrie in the early 1960s. Since that time, the screening of OEMs has been carried out worldwide. In the United States, newborn screening is a state mandatory public health program that ensures that all infants are screened for certain genetic conditions at birth. The screening eligibility table varies by state. The Advisory Committee on Genetic Disorders in Infants and Children advises the Minister of Health and the screening board to agree on human services, which currently consists of 34 core disorders and 26 primary disorders. The recommended panel includes many disorders related to amino acids (Table 7). Recommended uniform screening panel (RUSP) Argininosuccinate aciduria, citrullinemia type I homocystinuria (cystathionine-β-synthase), maple syrup urine disease, phenylketonuria/hyperphenylalaninemia, tyrosinemia IAdditional non-RUSP conditionsNonketotic hyperglycinemia (NKH), prolinemia, hyperammonemia/ornithinemia/citrullinemia (HHH)SecondaryDefects of biopterin cofactor biosynthesis citrullinemia II, hypermethioninemia, tyrosinemia II, tyrosinemia IIIList of amino acids disorders that are recommended by the Secretary of the Department of Health and Human Services (HHS) as part of state universal newborn screening (NBS) program effective July 2018.Quantitative amino acids analysis is an important tool for diagnosis of amino acids disorders and nutritional monitoring of individuals with already established diagnosis. Amino acids can be detected in most biological fluids, however, the most common fluids for congenital errors of metabolism diagnosis and monitoring are blood, plasma, and urine. In some cases, cyel fluid amino acid concentrations (CSF) are also diagnosed (Table 5). Although each disorder is characterized biosyncctively by abnormal levels of one or several amino acids, dosing a non-screening analysis, and explanations are not limited to those substances and range from a panel of nearly 40 amino acids and specific proportions. For example, along with plasma phenylalanine levels, it is important also to assess blood phenylalanine/tyrosine ratio can be used to distinguish between PKU and non-PKU hyperphenylalaninemia. The different chemical properties, a variety of normal estomic levels [17, 18, 19], age group variations and other factors detailed below represent a significant analytical challenge for amino acid analysis. Diet is one of the important factors that can affect amino acid levels [20, 21]. For example, consumption of meat and poultry leads to increased excretion β alanine and 1-methylhistidine. Therefore, blood collection intended for amino acid analysis is recommended after overnight fasting. Other factors such as urinary tract infections can significantly alter the profile of urinary amino acids[22]. Some drugs interfere with amino acid metabolism[23] or cause signal artifacts. Valproic acid, for example, can cause an increase in plasma glycine. Anti-clots used in the collection of samples may also contain interventional components[24]. For example, blood collection tubes containing sodium bisulfate in addition to heparin may bring S-sulfocysteine peaks, showing sulfite oxidase deficiency. Ethylenediaminetetraacetic acid additives (EDTA) in collection tubes can produce peaks positive for ninhydrin, so lithium-heparin coated tubes are strongly preferred for blood collection. An additional intervention factor in amino acid analysis is a hemolysis as it can lead to a decrease in arginine with a simultaneous increase of ornithine due to the activity of red blood cells arginase, and an increase in taurine release from leukocytes and letlets. Serum is usually not an option for analyzing amino acids, because blood needs to clot at room temperature in which asparagine is converted into aspartic acid and glutamine into glutamic acid. For urine analysis, a preferred 24-h urine collection, in other words, an overnight collection may be enough for diagnostic purposes. To avoid artifacts, no consive substances are added to the urine sample. Overall, in a prolonged storage sample glutamine and asparagine decreased while glutamic acid and aspartic acid increased simultaneously. Additional signs of prolonged storage are an increase in ethanolamine derived from decomposition of phosphoethanolamine, increased tryptophan, GABA and taurine. When csycephalolytic fluid is used for analysis, it must be free from blood infections, as it leads to a nonsomic increase of many amino acids and can mask diagnostic findings. Dosing amino acid analysis implies in a wide range of non-clinical fields such as biomedical research, bioengage engineering, food science and agriculture. Many analytical methods have been developed over the years, however, some of these methods are not cost effective and labor intensive and therefore are not applied in clinical settings. The purpose of the next paragraph is to describe the most common and widely used platforms in the field of laboratory medicine. In the early 50s, amino acids dosed the diagnosis became possible with Moore and Stein's publication on plasma amino acid separation with polystyrene resin columns[25] and further technical automation. This principle, known as ion exchange cylinthmics (IEC) with post-column diotomization, for a long time remains a gold standard for clinical amino acid analysis. Today, despite advances in methodo methodoths, ion exchange cylinthmics using lithium buffer systems, followed by private post-column resolution with ninhydrin and UV detection are still widely used in clinical settings. Prepare standard samples for analysis of IEC amino acids related to deproteinization with 35% (w/v) sulfosalicylic acid (SSA) added to biological fluids. It is recommended to use an SSA volume to 10 plasma volumes. A fixed amount of non-edomic amino acids as an internal standard is added to all samples. Commonly used internal standards ared-glucosaminic acid, S-2-aminoethyl-1-cysteine, norvaline, and norleucine, however, norleucine may interfere with argininosuccinic acid peaks. After a short incubation, centrifument and filtration, the sample is ready for injection and separation. In the IEC, separation is driven by ion interactions between amino acids and functional ligands that link to the fixed phase of the column. The cymromo column is filled with negatively electric plastic. The sample is loaded into columns in a low acidity pH and at this time, all amino acids carry a positive charge and interact strongly with the column. Manipulation with the lithium buffer component during running alters the pH and salt composition, and as a result, there is a change in the state of amino acid anolytic acid (Figure 5). When the isoelectric point reaches the amino acid is no longer charged and there is weak interaction with the charged column. Aspartic acid charge in pH.The complex separation of many amino acids is achieved based on the power of ion interaction. Amino acids with the weakest ion interactions to column start elute first. After column elution, the amino acid is mixed with a post-column realytic and optically detected. The most common and well-established post-column hydrolytic resolution is the reaction to ninhydrin that produces purple Ruhemann chromophore (λmax = 570 nm, Figure 6) for α amino acids and yellow products with second-class amines (λmax = 440 nm) for such as proline and hydroxyproline[27]. Ninhydrin reacts with amino acids to produce Ruhemann's purple color. The absorption intensity of the colorfully produced analyzer derived from every eluted amino acid is proportional to the concentration of amino acids in the biological fluid examined. Despite the fact that the IEC amino acid technique is very reproduced with a good linearity over a wide range, it suffered a long time for full amino acid profile (about 150 minutes), and lacked the same specificity as amino acid determination based solely on retention time. Moreover, the copper elution of some acid on the standard IEC method is observed. For example, homocitrulline co-elutes with methionine and makes HHH syndrome challenging. Moreover, allo-isoleucine, a diagnostic market for MSUD copper elutes with cystathionine. Argininosuccinic acid accumulates in patients with argininosuccinate lyase deficiency who have a retention period similar to leucine. Additional limitations of methodophthophation are the limited stability of ninhydrin (the recommended storage of working solution ≤1 month) which adds to the cost of analysis. In recent years, high-performance reverse-phase liquid chromofirs (RP-HPLC) and extremely high-performance liquid chromoths (UPLC) methods have emerged as an alternative to ion exchange chromoths. In RP-HPLC methods, separation is based on hydrolytic interactions between amino acids analyzed in the mobile phase and fixed hydro hydrolytic ligands attached to non-polar column fixation phases. RP-HPLC provides excellent resolution of molecules that are very closely related in a variety of chromotic conditions. For optical detection, derivatization with o-phthalaldehyde (OPA) can be used as a pre-column or a post-column reaction. In response, in the presence of thiols such as 2-mercaptoethanol, a stable fluorescent product is produced and can be detected with fluorimetry (stimulation of 340 nm and emission of 410 nm) or UV (340 nm) [28, 29]. Although reproducable and automated[30], the OPA derivatization method is not a good choice for detecting proline/hydroxyproline amino acids and containing sulfur. Alternative reatories for RP-HPLC with pre-column derivatization are phenylisothiocyanate (PITC, Pico-Tag commercialized by Waters)[31], dimethylamino-azobenzenesulfonyl-chloride (DABS-Cl)[32] and 9-fluorenylmethylchloroformate (FMOC-Cl). More advanced UPLC systems use small particle sizes (usually 1.7 μM) and high pH range stabilized columns. These systems use fewer solvents and are operated at high pressure allowing excellent resolution to be achieved in a short time frame and thus capable of reducing the turnaround time per sample. Narayan et al. analyzed 170 patient samples by pre-analyzing the 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate (AQC) derivatization (Figure 7) column followed by reverse-stage uplc[34] and comparing amino acid data with traditional amino acid analyzer that works through ion exchange chromocle. Research shows that the UPLC method is comparable to the reference IEC and therefore adapted to clinical laboratories. AQC reaction to amino acids. Peake et al. developed a modified RP-UPLC method and achieved better resolution for tyrosine, glycine, arginine and homocitrulline peaks. The improved method also provides advanced resolution to separate ornithine from mesocystathionine. There is high clinical significance for accurate ornithine analysis because ornithine levels are diagnosed for hyperornithinemia-hyperammonemia-homocitrullinemia syndrome (HHH). UPLC has been developed Advantage. Due to the short analysis time, the insertion of calibration before analyzing emergency samples with a particularly feasible turnaround time. In general, RP-UPLC reduces the turnaround time per sample, however, commercial ministry components have a very limited shelf life and therefore this method is not cost effective for clinical laboratories with small sample volumes. In general, ion exchange chromographs, RP-HPLC and RP-UPLC techniques have good reproduciability and high sensitivity in the low picomole range, however, all of them are done with optical detection. The main limitation of this type of detection is the lack of specificity because amino acids are determined based solely on retention time. This could potentially cause the wrong findings. For example, in a standard ion exchange cymonic method, ampicillin and amoxicillin are copper elute with phenylalanine and it can be reported as falsely increased. Recently, development and progress in the field of mass spectrum has led to the inclusion of parallel mass spectrum (MS/MS) as an alternative high througholytic and specific technique for amino acid analysis. It is also feasible to separate the amino acids by liquid cylinthmics before mass spectrum analysis, however, it is time consuming in clinical settings. Instead, parallel mass spectrum scanning is used to analyze high through throughomic, cost-effective amino acids. It should be noted that FIA-MS/MS is a screening analysis conducted extensively through the newborn screening initiative. For newborn screening, blood samples are usually collected on filter paper and a defined size (usually 3 mm) of the disk is punched out of paper and extracted. Initial tests require derivatization by butylation (Figure 8) to improve detection limits and minimize the inhibitory effect of ions in a complex biological matrix. Currently, to increase through throughte, some clinical laboratories skip the derivatization step. Samples of extraction and de-capitalization are introduced directly by injection into the mass spectrograph without syringes. Typically, 5–10 μl samples are injected into the flow solvent at a very low flow rate (20–50 μl). All screened amino acids (Table 8) are running fast at the same time while the typical running time is 1.5-2 minutes per sample. Each analyzed amino acid is assayed with the corresponding stable iso isotic labeling standard. Derivatization of alanine with n-butanol. Target amino acid/zInternal standardm/zAlanine146.12H4 alanine150.1Arginine231.213C,2H4 arginine236.2Aspartic acid246.22H3 aspartic acid249.2Citrulline232.22H2 citrulline234.2Glutamic acid260.22H3 glutamic acid263.2Glycine132.115N,13C glycine134.1Leucine/isoleucine188.22h3 leucine191.2Methionine206.22H3 methionine209.2Ornithine189.22H2 ornithine191.2Phenylalanine222.2213C6 phenylalanine228.2Tyrosine238.213C6 tyrosine244.2Valine174.22H8 valine182.2Amino acids analyzed by FIA-MS/MS for the standard newborn screening panel. Their stable iso iso iso isotholymity has internal standard labels. Iso isomic labeled standards are closely related to the structure of the analyzed amino acids and have the same physical chemical properties as the target amino acids, but can be distinguished by mass spectrum because they have different volume-to-charge ratios (m/z) (Table 8). They are added in known quantities and the reaction of each analyzed amino acid is standardized by the reaction of the appropriate internal standard. This type of normalization reduces a systematic error due to poor recovery and multiple matrix effects. The inclusion of internal standards also repairs a batch for batch transformation due to sample preparation and overall increases the accuracy and accuracy of the assay. Parallel mass spec spec spectral machines have five basic components: the source of ions in which all molecules are objects of soft ionization, a volume analyzer separates analyses based on the volume-to-build ratio (Q1), a collision cell where molecular ions encounter inert gases and undergo fragmentation (Q2), a second volume analyzer to separate debris generated in impact cells (Q3) and detectors. In cellular collisions, most butylated α-amino acids are screened to form a common and very specific piece of 102 Skin (Figure 9). Parallel mass spec spec specigraphs can then be set up to scan the constant mass difference of 102 skins and to create a spectrum of molecular ions derived from amino acids that have lost 102 skins in cellular collisions (Q2) (Figure 9). Butylated amino acids with a basal lateral chain such as ornithine, liquid citrulline ammonia and butyl formate in cellular collision (m/z 119). For glycine and arginine, the most intensive signal corresponds to the loss of 56 and 161 skins, respectively. All of these specific losses or transitions can be detected by different parallel and very specific parallel block spectral scans in single analysis. Presents the diagram of the parallel block spectral machine. Phenylalanine (such as butyl ester) takes 106 skin in cellular collisions. When the block spectral machine operates in neutral loss scanning mode, it scans Q1 and Q3 in sync. The mass difference of 102 skins (corresponding to a common neutral piece for most amino acids) passing through Q2 remains constant. The main limitation of FIA-MS/MS is its inability to distinguish m/z common amino acids such as leucine/isoleucine and hydroxyproline (butylated m/z 188), alanine/sarcosine (but m/z 146) and in a more extensive glutamine/lysine (butylated m/z 186), proline/asparagine (butylated m/z 172). In addition, FIA-MS/MS does not apply to cysteine and homocysteine analysis because these amino acids are unstable and react with cystine and homocystine forms (Figure 10). During ionization, cystine and homocystine produce dual-electric molecules and it complicates analysis. Sulfur amino acids and their disulfide. Due to its high sensitivity and there are many mass-based techniques available for amino acid analysis, although due to extensive sample preparation or limited quantities of covered amino acids, these methods are not widely used in clinical laboratories. Mass spectrometry (GCMS)[36] , mass spectrometry capillary electrolyse (CEMS)[37], Ion pairing (IP)-LC-MS/MS, HILIC-LC-mass spectrometry[38] and two column LC-MS/MS methods[39], paired ions (IP)-LC-HRMS (TOF)[40] can be successfully applied to bio-amino acid analysis albeit with some limitations. Initial diagnosis of amino acid disorders is based on clinical manifestations and biosynmbctively findings such as abnormal levels of specific amino acids (Table 1–6) or accumulation of downstream metabolic substances in biological fluids, however, these characteristics are very heterosexual and often nonsomic. The most common clinically indicated for the analysis of dosing amino acids in newborns and pediatric patients are coma, lethargy, convulsions and vomiting, innable developmental delays, and siblings with similar symptoms. Analysis of amino acids in plasma is also indicated as a configuration test to monitor abnormal newborn screening results. Hyposensitivity is characteristic for the most urea cycle disorders (Table 3) and therefore another strong sign for the analysis of amino acids in the blood plasma. Additional general biopsy indicators monitor the analysis of dosing amino acids as ketosis (high blood ketones and urine), acidosis (blood pH below 7.35) and lactic acidosis (high lactate secretion), alkaline (pH of blood above 7.45), polyuria, polydipsia (extreme thirst) and dehydration. Amino acid analysis is also an important tool in the diagnosis of muscle and liver diseases, neurological disorders, renal failure, autism spectrum disorders and nutritional disorders. Explanation of amino acid profiles is based not only on the degree of anolytic anolytic acid, but also in relation to sample identification, diagnostic rates (Tables 1 and 2) and correlation with the patient's clinical history. It is recommended to confirm the diagnosis by molecular analysis or in vitro enzyme testing (usually a biosynthese of the skin or tissue or blood cells). Currently, there are a number of treatments available aimed at a substrate and downstream product recovery balance (Figure 11). One of these approaches in this direction is to reduce the accumulation of substrates by limiting the diet. Nutritional therapy limits violations of amino acids or usually total protein consumption through the provision and monitoring of all essential ingredients to meet dietary requirements. For example, medical foods specifically for PKU affected individuals have a very insignificant amount of phenylalanine, but total protein supplementation is required for normal growth, development and nutritional status. Another example is MSUD nutrition management that limits the amount of branched amino acids but provides the majority of the protein needed in the standard diet. Treatment strategies in amino acid disorders. Amino acid disorders are often manifested by the accumulation of toxic metabolic substances downstream. For example, urea acid disorders are characterized by life-threatening hypertension (accumulation of ammonia). Treatment of the elimination of toxic chemicals is aimed at reducing the production or increasing the secretion of chemical substances. To reduce hyperammonemia, sodium benzoate and phenylbutyrate are used to increase ammonia secretion (Figure 12) and to skip the urea cycle metabolic mass[42,43]. Another example is an approach to reducing the production of succinylacetone, a neurot toxin accumulated in tyrosinaemia I. Nitisinone (NTBC) treats a mass formation of fumarylacetoacetate and its next conversion to succinylacetone[44, 45]. Eliminate toxic ammonia. In cyclical disorders urea ammonia cannot be converted into urea, but otherwise can be converted into glutamine and glycine. Ammonia scavengers phenylbutyrate and sodium benzoate react with glutamine and glycine and thus eliminate excess ammonia. Phenylglutamine and hippurate are excreted in the urine. If as a result of mutations, a particular enzyme retains its remaining activity, it can be stimulated by a co-factor or co-factored pre-supplementation. This concept applies in the treatment of tetrahydrobiopterin deficiency (Figure 2)[46, 47], remethylation defects (Figure 4)[48] and cystathionine beta-synthase deficiency (Figure 4). In some amino acid disorders, even part of the metabolic block blocks the metabolism of a downstream metabolic substance needed to meet metabolic requirements. In these cases, supplementation of essential products is necessary. For example, as part of the management of urea cycle disorders,l-arginine andl-citrulline is administered [43]. This helps to reduce too much protein catabolism, due to low arginine levels. In conclusion, amino acid disorders are a group of congenital errors of metabolism with very different clinical and biosynpolar manifestations. Clinical manifestations often include severe neurological symptoms, growth, and retarded development. Most of the condition-related amino acid disorders are included in the newborn screening program to facilitate early diagnosis and treatment of the disease early. The analysis of the concentration of ingamine acids is an important tool in the diagnosis and clinical management of congenital errors of amino acid transformation. A small set of amino acids is analyzed in newborn screening by a parallel mass spectrum and leads to the detection of affected infants even if they do not present with symptomatic disease. A more comprehensive, dosing analysis of amino acids includes an analysis of nearly 40 amino acids. Before analyzing and explaining the results, pre-analytical variables such as fasting status and drug treatments should be taken into place to avoid mis-reported findings. A Common sample preparation method for analyzing dosing amino acids is to acidize specimens with a small amount of known concentrated acid, such as sulfosalicylic acid to precipitate proteins and large molecules, followed by centrifumosis, leaving water-soluble amino acids in super-natural for analysis. A variety of analytical methods have been developed over the past 60 years, and scientists have achieved significant achievements in the fields of derivatization, cymosis and mass spectrum, however, the method of ion exchange cymosis remains the gold standard technique in this field. It is expected that more advanced techniques will be developed targeting important clinical laboratory requirements such as reduced sample pre-processing, linearity across a large concentration range for more than 40 amino acids, increased automation, high sensitivity, shorter running time and improved specificity. Improvements to this method will facilitate the process of diagnosis and monitoring of treatment of amino acid disorders. The field is also expanding into more exploring platforms such as genome-wide sequences and un targeted transformation. Although these methods have some limitations in clinical settings[1, 49], they facilitate the identification of new genes, the detection of new biomarkers and disease associations, and thus strongly promote this field. The main therapeutic goal for amino acid disorders is to normalize the imbalance between the substrate and its downstream products and to avoid the accumulation of toxic substances. At the same time, nutrition management must meet the basic dietary requirements for normal growth and development. Although for many amino acid disorders current treatments do not provide a cure, they significantly improve the quality of life. It is expected that in the coming years, advances in methodosis will lead to a greater understanding of IEM and especially amino acid-related disorders that will help further improve the outcome of the disease.2033total chapternext chapterBy Wojciech Smętek, Jacek Węgrzyk, Agnieszka Klama-Baryła, Wojciech Łabuś, Małgorzata Kraut, Michał Szapski, Mariusz Nowak and Diana KitalaFirst chapterBy Selvan Ravindran , Rutuja Rokade, Jitendra K. Suthar, Pooja Singh, Pooja Deshpande, Rajeshree Khambadkar and Srushti Utekar We are IntechOpen, the world's leading open access book publishing house. Built by scientists, for scientists. Our readers include scientists, professors, researchers, mailers and students, as well as business professionals. 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