Metabolic encephalopathies in children: A pragmatic diagnostic approach based on literature analysis

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Abstract

Inborn errors of metabolism (IEM) in the general population are rare diseases. However, from the perspective of general pediatrics and pediatric intensive care units (PICUs), they are becoming a significant challenge both diagnostically and therapeutically. Clinically, there is a useful division of IEMs with neurological manifestations into 2 categories: acute and progressive encephalopathies. The extent of individual IEMs in these 2 groups varies, requiring different diagnostic strategies. Despite progress in development of diagnostic tools in IEM, initial diagnosis is made on the basis of basic laboratory tests, neuroradiological findings and metabolic screening. In settings of shortage of diagnostic resources and under time pressure, rational decisions should be made based on available clinical data. The text discusses diagnostic aspects of IEM presenting as metabolic encephalopathies, highlighting their significance in the context of general pediatric care and intensive care units (ICUs), and the challenges associated with diagnosis. It should be noted that the paper does not include a discussion of epileptic encephalopathies of IEM etiology, although some cases of metabolic encephalopathies may also present initially as epileptic encephalopathy.

Key words: inborn errors of metabolism, metabolic encephalopathy, metabolic screening

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Introduction

In the general population, inborn errors of metabolism (IEM) are rare diseases. However, from the perspective of general pediatrics and pediatric intensive care units, they are becoming a significant challenge both diagnostically and therapeutically. Clinically, there is a useful division of IEMs with neurological manifestations into 2 categories: acute and progressive encephalopathies. The extent of individual IEMs in these 2 groups varies, requiring different diagnostic strategies. The text discusses diagnostic aspects of IEM presenting as metabolic encephalopathies, highlighting their significance in the context of pediatric care and the challenges associated with diagnosis.

It should be noted that the paper does not include a discussion of epileptic encephalopathies of IEM etiology, although some cases of metabolic encephalopathies may also present initially as epileptic encephalopathy.

Metabolic encephalopathy: Definition and scale of the problem

Encephalopathy is a non-specific term that generally refers to disorders of central nervous system (CNS) function. These disorders are usually characterized by symptoms such as impaired consciousness and cognitive abilities, and may be accompanied by symptoms related to the pyramidal, extrapyramidal or seizure systems.

Etiologically, 2 main groups of encephalopathies can be distinguished: acquired and inborn, while from a clinical perspective, we distinguish acute and chronic encephalopathies. Metabolic encephalopathies result from inborn metabolic errors, which manifest themselves in both acute and chronic, progressive forms.

The overall incidence of IEM is 50.9 cases per 100,000 live births, with a higher prevalence in Middle Eastern countries. The approximate mortality rate in this group of patients averages 33%, but with significant differences depending on the level of national income. In highly developed countries, the rate fluctuates between 2% and 23%.[1] There are no separate data on the proportion of cases manifested by acute or chronic encephalopathy in the total number of IEM cases. An attempt to estimate the epidemiological size of this phenomenon in the context of acute encephalopathies is provided by information on the percentage of patients with IEM hospitalized in intensive care units (ICUs).

In a study conducted by Maksoud et al., in a group of 30 patients with encephalopathy of unknown cause admitted to the ICU within a year, it was found that 10 of them showed abnormal biochemical test results indicative of IEM. Of these cases, 4 hospitalized patients (13.3%) had organic aciduria, 4 (13.3%) had probable mitochondrial disease, 1 (3.3%) had a urea cycle defect, and 1 (3.3%) had nonketotic hyperglycemia.[2] In contrast, in a study by Magdy et al. of 308 infants with initial suspected IEM, a metabolic defect was eventually confirmed in 93 patients (30.2%).[3]

A large study by Lipari et al. involving analysis of 4,459 pediatric ICU admissions over a 10-year period found that IEM accounted for 2% of hospitalizations (88 cases in 65 children). Of these cases, 62 admissions (70.4%) were associated with metabolic decompensation, which manifested clinically as encephalopathy. There were 8 deaths in this group of patients.[4] Results similar to these were also described by Couce et al., who observed 31 cases of patients with IEM out of 1,104 admissions to the pediatric ward over an 8-year period, accounting for 1.63% of all hospitalizations. Of these cases, 18 required intensive care, and 12 patients had a clinical picture of acute encephalopathy that did not require ICU care. The mortality rate among patients with IEM was 10.3%.[5] It is noteworthy that both of these latter analyses are from highly developed countries where there is a well-developed IEM diagnostic base based on population-based screening, which may influence the lower reported rate of cases leading to metabolic decompensation.

Metabolic encephalopathies can manifest themselves at any stage of life, but most often are observed in the first few years. As symptoms appear later, cases are more likely to fall into the group of chronic, progressive diseases associated with a defect in the metabolism of complex molecules. In the study by Lipari et al., the average age of patients with IEM hospitalized in the acute-onset state was 3 years (ranging from 3 days old to 21 years), with the average age of diagnosis at 3 months.[4]

In the context of acute encephalopathy, from a clinical perspective, it is useful to divide the disease into 2 main groups:

1. Intoxication group (organic acidurias, urea cycle defects);
2. Energy failure group (fatty acid oxidation disorders, mitochondrial diseases).

In the available studies, the syndromes of intoxication (IG) and energy production disorders (EFG) represent comparable numerical groups of hospitalized patients. In a study by Lipari et al., the numbers of patients admitted were 23 and 21, respectively, out of 65 hospitalized for encephalopathy.[4] Similar proportions of patients with IG and EFG are reported in other studies: 5 and 6 out of 11 hospitalized with IEM, respectively[6] and 5 and 4 out of 10 hospitalized with IEM.[1]

Clinical picture

In IG, disorders of consciousness (coma) are the leading symptom, which affects almost all patients. Disorders of consciousness are usually preceded by the onset of infection and vomiting. More than half of the patients have seizures, 20% patients have hypotonia and 10% have muscular hypertonia.[1]

In EFG, due to impaired fatty acid oxidation, the clinical presentation at the onset of encephalopathy is similar to IG. In Polish conditions, most patients at the time of admission already have a confirmed diagnosis (screening).

In the case of mitochondrial diseases, the clinical picture is richer, and the course of the disease itself is an exacerbation of the course rather than a sudden manifestation of the encephalopathy – respiratory failure or respiratory disorders of the hyperventilation type, dehydration, heart failure in patients with developmental problems, hypotonia and muscle weakness. The course of the disease is most often exacerbated by infections. From the point of view of physicians working in pediatric wards, it is important to report that the most common symptom in this group of patients on admission was fever.[8]

In view of the highly non-specific clinical picture of a patient with acute metabolic encephalopathy (this problem does not, of course, apply to those with already diagnosed metabolic disease), the correct diagnosis of the causes of the encephalopathy can be guided by basic tests.[9,10] The most common abnormalities found in this group of patients are metabolic acidosis (75–78% of patients), lactic acidosis (50–66%), hyperammonemia (33–62.5% of patients), and ketonuria (22–37% of patients).[8,11] Hypoglycemia as an abnormality in metabolic encephalopathies was reported in only 1 study (37.5%) with a comparable percentage of hyperglycemia (25%).[8] The same study also reported a high percentage of hyperuricemia in acute metabolic encephalopathies (87.5%). A high value for this parameter also occurred among acute non-metabolic conditions (30.8%), indicating the severity of catabolism in a given patient regardless of its cause. Metabolic acidosis is equally non-specific, occurring in a significant percentage of patients referred to ICUs. The laboratory examinations listed above should also be performed when patients are hospitalized already with a diagnosis of any of the diseases from the group of intoxication syndrome. The occurrence of the above abnormalities indicates a metabolic breakthrough or a significant risk of its occurrence.

Neuroimaging studies are an integral part of diagnosing encephalopathies. In the case of metabolic encephalopathies, computed tomography (CT) or magnetic resonance imaging (MRI) scans often reveal changes, but practically only in 2 cases led to the suspicion of specific diseases: glutaric aciduria type 1 and Leigh syndrome.[12]

A CT scan of the head often reveals cerebral edema and atrophy, with total abnormalities found in 68% of studies.[2] A brain MRI provides more informative results: atrophic lesions (44%), white matter lesions (19%) and lesions in the basal nuclei (7%). Abnormalities were present in 44% of all patients.[2]

Neuroimaging studies are important in the differential diagnosis of encephalopathies and in making initial therapeutic decisions, but when analyzed in a specific clinical context, they can help in the metabolic diagnosis. Of the other imaging studies, we should consider evaluation of the heart for cardiomyopathy (mitochondrial diseases), the presence of pericardial fluid and arrhythmias (fatty acid oxidation disorders) or abdominal ultrasound – hepatomegaly.

The basis of metabolic diagnosis in encephalopathies of unknown cause are metabolic screening tests:

1. Profile of acylcarnitines in dry blood drop using tandem mass spectrometry (MSMS) method;
2. Urine organic acid profile using gas chromatography-mass spectrometry (GCMS) method;
3. Plasma aminoacidogram.

The above tests make it possible to diagnose syndromes of intoxication, listed as following:

1. Organic aciduria;
2. Defects of the urea cycle;
3. Disorders of fatty acid and ketone metabolism;
4. Disorders of amino acid metabolism;
5. Exacerbation of the course of mitochondrial diseases.

In the case of mitochondrial encephalopathy exacerbation, these tests do not allow a confident diagnosis; there is no unequivocal biochemical marker in mitochondrial diseases. The lactic acidosis associated with these diseases occurs in about 60% of cases and is usually associated with hyperalaninemia.

Results of metabolic screening tests are necessary to conduct targeted treatment in IEM. The problem lies in the rapid availability of the tests. Most hospitals lack adequate diagnostic facilities and samples must be sent to other centers. Samples for testing should be secured immediately after the child's hospitalization, even in the case of newborns who have already undergone population screening and whose test results are still unavailable. It is possible that the tested disease markers have not yet accumulated in sufficient quantity to give a positive screening result.[13] Widespread genetic testing such as targeted gene sequencing panels and whole exome sequencing (WES) are currently not applicable to the clinical practice for differential diagnosis of acute metabolic encephalopathies. This limitation is primarily due to the time factor – the result is obtained too late to affect therapeutic decisions by causing a change in perspective.

Nevertheless, in any case of acute encephalopathy of unknown cause, a DNA sample should be secured for such testing, in case of an unsuccessful course of the disease and for subsequent confirmation of the diagnosis.[14]

Chronic metabolic encephalopathies

Chronic metabolic encephalopathies (CME) are a group of diseases that are the domain of pediatric departments (except for exacerbations of mitochondrial diseases) and should be diagnosed according to the standards of classical differential diagnosis. Chronic metabolic encephalopathies are characterized by:

1. Progressive neurological deterioration; the period of observation can vary depending on the disease. Generally, the older the age of first manifestation, the slower the disease progression. An important element of follow-up is the progression of changes on brain MRI;
2. Gradual loss of cognitive or psychomotor abilities;

3. The appearance of additional neurological symptoms;
4. Lack of external causes of encephalopathy (inflammatory, traumatic, toxic).

The magnitude of the CME is represented by the percentage of IEM diagnoses among patients with progressive encephalopathies. In 2 cross-sectional studies, the percentage of IEM among CME was 75%[15] and 62.5%.[16] In 1 study, the percentage was as high as 88.9%.[17] In a study by Stromme et al., the percentage of IEM among patients with encephalopathy was 33.3% (88 patients were identified), giving an incidence of 2.14/100,000. However, this study analyzed all encephalopathies, including those with acute manifestations.[18]

The spectrum of IEM with neurological manifestations, including CME, is considerable, some with multi-organ manifestations. The exception is protein glycosylation diseases, where CNS dysfunction is rarely progressive, although the course can be extremely severe from the perinatal period onward, with significant mortality also from extracerebral causes (cardiac and hematologic).[19,20]

There are no data on the age distribution of CME manifestation. The data that Stromme et al. cite in their paper are cumulative data, which also include encephalopathies classified as acute in this study. In such a compilation, the percentage of age-related encephalopathies is 45.5% for 1 month-olds, 21.8% for infancy, 27.2% for 1–5 years, and 5.5% for 6–12 years.[18] The reported data indicate a significant percentage of acute encephalopathies in young children, as, for example, the age of manifestations of the most common lysosomal diseases among CME is 2 years.[21]

In the analysis of 2,152 reports from PubMed on progressive cognitive and neurological disorders, 85 cases had a metabolic basis, of which 34/85 (40%) were specifically lysosomal diseases, 15/85 (17.6%) diseases from the group of disorders of metabolism of nitrogen-containing molecules (organic acidurias, urea cycle defects – encephalopathies with acute presentation), 15/85 (17.6%) disorders of vitamin, cofactor and metal metabolism, 14/85 (16.5%) mitochondrial diseases, 2/85 peroxisomal diseases, and 2/85 disorders of lipid metabolism with 1 case each of glycosylation, carbohydrate and tetrapyrrole disorders.[22] Regardless of the methodology of analysis, the most common causes of CME are lysosomal diseases followed by mitochondrial disorders, peroxisomal disorders, congenital disorders of glycosylation, and disorders of purine and pyrimidine metabolism.

The clinical presentation of CME is included in the above criteria. The most commonly associated neurological symptoms are epilepsy (79%) and psychomotor or intellectual developmental delay (39%). Disorders of muscle tone, nystagmus, and sensory or movement disorders are also observed. In some diseases, extra-neurological symptoms are also present, which, for example, in some mucopolysaccharidoses precede neurological symptoms and are often the starting point of diagnosis.

Of the neuroimaging studies, MRI provides the most information. The result of the study in individual cases may indicate a specific diagnosis such as glutaric aciduria type 1 or X-linked adrenoleukodystrophy (XALD). Receiving such suggestions also depends on the experience of the radiologist and the collaboration with the patient's treating physician, which means that tests should not be evaluated in a clinical vacuum. In other cases, MRI guides the diagnosis of diseases with predominant involvement of the white matter, gray matter or basal nuclei. According to Wenger et al., a metabolic background of the disease is indicated by symmetrical changes in brain MRI, especially with associated features[23]:

1. Pattern of change characteristic of the IEM;
2. Brain MRI does not correspond with hypoxic-ischemic changes;
3. Isolated or dominant cerebellar or brainstem involvement;
4. Freshly revealed acute or chronic lesions;
5. In newborns, congenital lesions and/or reduced brain volume;
6. Progressive brain atrophy;
7. Malformations with acquired lesions.

White matter involvement is frequently observed in CME, which is consistent with the predominance of lysosomal diseases in this group of patients. However, it should be remembered that lysosomal diseases are a large group of genetic metabolic disorders with heterogeneous clinical presentation and patterns of CNS involvement.

In an analysis of 5,166 MRI images with white matter involvement, leukodystrophy was present in 5% of all images. Autoimmune diseases predominated (23%) and often required differentiation from IEM.[23]

Nonspecific lesions may be a problem in patients who have undergone testing for causes other than CME (18%). In the absence of a complete clinical analysis, they may be the cause for further unnecessary and traumatizing diagnosis.

Characteristically, in the cited study, all instances of white matter involvement in this group of patients were located supratentorially.[23] If leukodystrophy is found, further radiological analysis should differentiate between hypomyelination, demyelination and dysmyelination. The presence of additional changes such as cysts, contrast enhancement or involvement of the nucleus accumbens can further guide the diagnosis.[24,25] Magnetic resonance spectroscopy reveals nonspecific lesions and indicates the diagnosis only in the case of deficits in creatine synthesis and transport.[27]

Baseline tests in CME are mostly not diagnostic. However, in rare cases they may be the basis for diagnosis, such as low copper and ceruloplasmin levels in the Menkes disease or low uric acid and homocysteine levels in molybdenum cofactor deficiency.

These useful metabolic screening tests are also rarely diagnostic in CME, but are nevertheless necessary since patients in between acute episodes of intoxication

demonstrate chronic symptoms, including consequences of past exacerbations. In view of the prevalence of lysosomal disease in CME, tests of lysosomal enzyme activity in a dry blood spot or whole blood, supported by assessment of oligosaccharide or glucosamine excretion, are most useful. The above does not cover the full spectrum of tests available for the diagnosis of lysosomal diseases, but from a clinical point of view, it is a good diagnostic starting point.

The desirable situation is the suspicion of a specific IEM. When peroxisomal diseases are suspected, of great value as a first-line test is the concentration of very long-chain fatty acids, useful in the most common diseases of this group such as XALD and disorders of peroxisome biogenesis.

Confirmation of the diagnosis is provided with genetic testing, especially next-generation sequencing (NGS), in the absence of a specific suspicion or narrowing the suspicion to a group of diseases. In a study by Salman et al., out of 126 genetic tests performed in suspected IEM, positive WES results helped establish the diagnosis in 22/45 patients (48.9%), panel testing in 8/13 (62%), and targeted genetic testing in 50/67 (75%), indicating the role of precise clinical analysis in ordering this type of testing.[27] For neurogenetic diseases in general, the reported efficiency of WES ranges from 16 to 68%, depending on the study.[28] It is interesting to compare the efficiency of diagnosing IEM using WES (whole exome sequencing) and MSMS as first-line methods. The study was performed on samples from 4.5 million newborns. The sensitivity of WES was 88% with 98.4% specificity compared to the 99% sensitivity and 99% specificity of the MSMS method.[29]

Summary

Inborn errors of metabolism in the general population are rare diseases, but from the perspective of general pediatrics or ICUs, they are already a significant epidemiological problem. There is a lack of epidemiological data for Poland, partly due to the lack of a rare disease registry. Estimates based on literature reports put the percentage of IEM at 1.63–2% of those hospitalized in ICUs. In clinical practice, these are patients with acute metabolic decompensation or acute encephalopathy. These data come from highly developed countries with a well-developed screening system for inborn metabolic diseases.

A separate issue is the percentage of progressive encephalopathies of metabolic origin that usually do not require acute hospitalization. Data report 33.3–89.8% of all progressive encephalopathies, with a frequency in the general population of 2.14/100,000 people, making CME a significant problem in the practice of metabolic or neurological departments.

Inborn errors of metabolism with acute encephalopathy manifestations are primarily disorders of small molecule metabolism and they include organic acidurias (OA), urea cycle defects (UCD) and fatty acid oxidation disorders (FAOD). Of these diseases, OA and FAOD are largely covered by screening. In practice, this means that the preponderance of patients in these groups are newborns with early manifestations of the disease (before screening results are available) and children with an already established diagnosis and disease exacerbation. In the case of UCD in Poland, screening includes patients associated with increased levels of citrulline (2 enzymatic defects), which does not allow neonatal screening to identify ornithine transcarbamylase deficiency, the most common enzymatic defect in UCD.

Baseline laboratory investigations can give important clues to the metabolic background of the disease. The most common abnormalities include hyperammonemia, acidosis, lactic acidosis, and hyperketonemia. The clinical presentation of acute encephalopathy and the above abnormalities require consideration of IEM in therapeutic management.

Considering the IEM as the cause of acute encpehalolpathies, the basis for the diagnosis is the profile of acylcarnitines in a dry blood drop using MSMS, the profile of urinary organic acids by GCMS and the plasma amino acids profile. The latter test is crucial in the differential diagnosis of UCD. These tests should also be performed in any acute encephalopathy, despite a negative screening result.

Lysosomal diseases account for the largest percentage of CME. The most common of these are neuronal ceroid lipofuscinosis (CLN), Niemann–Pick disease type C (NPC), mucopolysaccharidosis type 3 (MPS3), and metachromatic leukodystrophy (MLD).[30] Lysosomal diseases account for the largest percentage of CME. The most common of these are CLN, NPC, MPS3, and MLD. The basic biochemical diagnostic methods for lysosomal diseases include the measurement of enzyme activity, substrate concentrations and alternative reaction products for particular diseases.

The choice of test depends on the patient's clinical evaluation and radiographic findings and can be made after consultation with a metabolic pediatric specialist. A summary of tests necessary for the diagnosis of metabolic encephalopathies is given in Table 1.

Broad-spectrum genetic testing plays an important role in CME. However, its efficiency in diagnosing progressive metabolic encephalopathy, a component of most IEMs, remains lower than targeted genetic testing, emphasizing the importance of clinical analysis of the disease course.

For acute presentations of IEM, there are attempts to use rapid WES diagnostic techniques, but metabolic studies are still the basis of diagnostic decision-making. The exception are mitochondrial diseases, in which genetic testing is the first choice in the absence of clear biochemical markers.

Applications

- Inborn errors of metabolism that present as encephalopathies are rare diseases in the general population, but are a significant concern in pediatric departments and ICUs.

Table 1. The usefulness of biochemical tests in the diagnosis of different groups of IEM

Type of test	Acute metabolic encephalopathies	Progressive metabolic encephalopathies
Urine		
Ketones	+	–
Organic acid profile method – GCMS	++	–/+
Glycosaminoglycans	–	+
Oligosaccharides	–	+
Profile of purines and pyrimidines	–	+
Blood		
Ammonia, gasometry, lactic acid	++	–/+
Profile of acylcarnitines in a dry blood drop method – MSMS	++	–/+
Aminoacidogram	++	–/+
Homocysteine	–/+	+
Transferrin isoforms	–	+
VLCFA	–	+

IEM – inborn errors of metabolism; GCMS – gas chromatography-mass spectrometry; MSMS – tandem mass spectrometry; VLCFA – very long-chain fatty acids.

- In every case of encephalopathy of unknown origin, metabolic background of the disease should be considered. The extent of first-line metabolic testing should vary between acute and chronic encephalopathy patient groups.
- Baseline laboratory investigations often reveal key abnormalities such as hyperammonemia, acidosis, lactic acidosis, and hyperketonemia. If these abnormalities coincide with the symptoms of acute encephalopathy, it's worth considering IEM as a part of therapeutic management.
- Diagnosis of acute metabolic encephalopathies relies on specific tests, including profiling acylcarnitines in dry blood drops using MSMS, urinary organic acid profiling with GCMS and plasma amino acid profiling. These tests are essential even if screening results are negative.
- Broad-spectrum genetic testing (WES, NGS) plays a crucial role in diagnosing CME. However, its efficiency is still lower than targeted genetic testing, emphasizing the importance of clinical analysis. In acute presentations of IEM, metabolic studies remain the primary diagnostic tool, except in mitochondrial diseases, where genetic testing takes precedence.

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