SHORT COMMUNICATION

Metabolic cause of Reye-like syndrome

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Abstract

The most frequent metabolic cause of Reye-like syndrome is medium chain acyl-CoA dehydrogenase (MCAD) deficiency.The authors describe a gypsy boy who was repeatedly hospitalised due to symptoms of Reye-like syndrome (serious hypoglycemia, loss of consciousness, seizures, increased values of aminotransferases, decreased values of free carnitine). The diagnosis of MCAD deficiency was established by analysis of plasmatic acylcarnitines by use of tandem mass spectrometry. DNA analysis proved the most common K329E (G985) mutation in gene for MCAD deficiency in homozygous state. The authors have emphasised the advantage of tandem mass spectrometry in the diagnosis of disorders of fatty acid ß-oxidation. This highly sophisticated method can detect most of these disorders from dry blood spots disregarding the symptoms and type of mutation. *(Short communication)*

Reye syndrome (RS) appeared suddenly in 1963 as a life-threatening state with encephalopathy and fatty degeneration of the liver (8). In the 1970′s and 1980′s RS was the epitome of pediatric intensive care. From the etiologic point of view, a number of epidemiologic case-control studies demonstrated an association between RS and the ingestion of aspirin (12). Later its occurence began to decrease significantly. It was assumed that this decrease was accompanied by recommendation to restrict aspirin use. RS, however, has gradually disappeared from countries such as Australia, which had not used aspirin since the 1950′s (7) and France and Belgium, which continued to use aspirin in children without change (9). These facts have doubted the causal relation between use of aspirin and the origin of RS.

By the late 1980′s, a number of inborn errors of metabolism were discovered that could mimic RS clinically, biochemically, and pathologically. The term RS was replaced by the term Reye-like syndrome, while its possible cause was most frequently involved the disorders of ß-oxidation of fatty acids.

Case history

The boy of gypsy origin was the first child of healthy parents, born at term with a weight of 2,700 g and length of 49 cm. He had been doing well, breast-fed one month, later on an ordinary infant formula.

At 15 months of age during respiratory illness, which was treated by antibiotics, the child repeatedly vomited and had low food intake. He was admitted at University Children ’s Hospital following mental confusion and tonic and clonic seizures. On examination extreme hypoglycemia of 0.6 mmol/l. was detected. After intravenous administration of glucose, clinical state gradually recovered, as well as the level of glucose. The biochemical tests revealed increased values of liver tests: AST 2.05 μkat/l and ALT 2.14 μkat/l. The level of free carnitine was significantly decreased (11.7 μmol/l*)*. The patient was discharged with suspicion of disorder of fatty acid oxidation with recommendation of frequent feeding. Three months later symptoms of Reye-like syn-

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drome repeated (mental confusion, severe hypoglycemia of 1.8 mmol/l, increased values of aminotranferases and decreased level of free carnitine of 17.5 μmol/l.) Analysis of urine , collected during acute attack, by gas chromatography/mass spectrometry (GC-MS) revealed no pathological findings. Four months later, Reye-like symptoms repeated again during infection with febrile state and vomiting. The patient was brought unconscious to the Intensive Care Unit. Dry blood spot was sent for acylcarnitine analysis (Freiburg). Tandem mass spectrometry (Tandem MS) revealed incresed levels of C-8 acylcarnitines while the ratio of C8/C10 = 5.3 (normal <5) and the ratio C8/C2 = 0.08 (normal <0.02) at a very low value of free carnitine of 1.6 μmol/l (normal <15). The carnitine loading test (100 mg/kg) unambiguously increased the levels of C6, C8, C10 and C12 acylcarnitines, while the ratio C8/C10 = 12, C8/C2 = 0.22 and C8/C12 = 103 (normal <5) at normal value of free carnitine of 34 µmol/l. By GC-MS additional examination of urine revealed increased values of glycine conjugates (hexanoylglycine, isohexanoylglycine, phenylpropionylglycine and suberylglycine), the test for 3-phenylpropionate was positive and direct DNA analysis proved homozygote for 329E (G985) mutation. Both parents were proved to carry this mutation in heterozygous form. Despite the recommended diet, another attack repeated in 3 months. After inclusion of carnitine into therapy, Reye-like episodes did not occur.

Discussion

The list of diseases that could mimic RS became quite extensive (6). The most important if these mimickers of RS were the metabolic disorders, especially the fatty acid ß-oxidation defects. In recent years tremendous progress has been made with respect to the enzymology of the mitochondrial fatty acid ß-oxidation machinery and defect therein. A number of new mitochondrial ß-oxidation enzymes have been identified and introduction of tandem MS for the analysis of plasma acylcarnitines has greatly facilitated the identification of patients with a defect in fatty acid oxidation (11).

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is one of the most frequent genetic metabolic disorders. The highest occurence of MCAD deficiency is in the northwest Europe (10). This disease is associated with a significant risk of sudden death or permanent damage of the central nervous system. A remarkable significance is ascribed to early diagnosis, as a simple and effective therapy can be applied. So far, the diagnosis of this disorder has been based on clinical and laboratory symptoms of Reye-like syndrome (mental confusion, increased values of aminotransferases, hypoketotic hypoglycemia, decreased value of free carnitine), the detection of increased urinary excretion of dicarboxylic acids and other metabolites by use of GC-MS, provocation tests, measurement of enzymatic activities in cultivated fibroblasts and lymphocytes. The molecular diagnosis of this disorder had a remarkable position, since the dominant K329E mutation (A985G) accounted for 80—90 % of all disease-associated alleles in MCAD deficiency patients in various populations of northwestern Europe (3). Frequency of heterozygotes with K329E (A985G) mutation vary in many European countries from 1/50 to 1/120, the fact of which responds to approximate incidence from 1:8,000 to 1:40,000 live-born infants (10). The frequency of carriers of this mutation in Czech Republic is approximately 1/250 (5, 10). The main problem in classical diagnosis by means of GC-MS is the collection of urine in the acute attack of the disease, since only during the acute attack it is possible to detect the dicarboxylic aciduria with typical pathologic metabolites. During the asymptomatic period between the attacks, results of laboratory tests are usually not so much expressed, or they are within the range of reference values (13). The diagnosis assessment by means of GC-MS was not successful in our patient. It was successful by use of tandem MS, which currently represents a new multianalytic method appropriate especially for the diagnosis of the disorders of fatty acid ß-oxidation. Its advantage resides on establishing the diagnosis from a dry spot disregarding the symptoms, type of mutation and therapy. In dubious cases, it is necessary to carry out the carnitine loading test (11), which, as in our case, unambiguously reveals the presence of pathological acylcarnitines. Tandem MS is currently replacing a whole spectrum of methods, including the classical GC-MS method, which have so far been used for screening of inborn errors of metabolism (1).

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