

FEATURES OF THE ENDOCRINE-METABOLIC PLURIMALFORMATIVE SYNDROME

Mariana Boia¹, Aniko Manea¹, Oana Bilav²

Abstract

Introduction: Inherited metabolic disorders refer to different types of medical conditions that result in metabolism problems. They involve great complexity of the underlying pathophysiology, biochemical workup, and analysis and have complicated therapeutic options for management. They are disorders of great importance to physicians treating newborns because rapid diagnosis and appropriate treatment of these conditions are directly related to the patient's outcome in terms of mortality and morbidity. Some metabolic disorders can be diagnosed by routine screening tests done at birth, others are identified only after a child or adult shows symptoms of a disorder. A wide range of tests are required for the diagnosis of inborn errors of metabolism and the level of clinical and biochemical experience required is often substantial. There are hundreds of different genetic metabolic disorders, and their symptoms, treatments, and prognosis vary widely.

Case presentation: The 4 month old newborn baby boy, admitted to the IC Premature Children's ward at "Louis Turcanu" Emergency Hospital, diagnosed ventriculomegaly and agenesis of corpus callosum, seizure type EEG is investigated to establish the etiology of diseases, *is suspected* for an Inherited Metabolic Disease.

Conclusions: Molecular genetic analysis has become a necessity due to the numerous clinical forms existing in the specialty literature. Confirmation of the diagnosis will allow the appreciation of the prognosis and of the measures that need to be taken in order to improve the child's quality of life. It requires multidisciplinary monitoring (pediatrician, endocrinologist, geneticist, neuropsychiatrist).

Key words: metabolic disease, genetics, ventriculomegaly, agenesis of corpus callosum

Introduction

Though individually congenital metabolic diseases are relatively rare conditions, as a group there is a vast and diverse collection of diseases that are a significant cause of morbidity and mortality worldwide. Onset is usually in the neonatal period and childhood but can occur at any time, even in adulthood. The diagnosis

does not require extensive knowledge of biochemical pathways or individual metabolic diseases. An understanding of the major clinical manifestations of congenital metabolic defects provides the basis for knowing when to consider the diagnosis. There may be several inborn errors of metabolism that are entirely incompatible with life and lead to intrauterine fetal death.

Because of the many different errors of metabolism diagnostic tests are used for screening.

Inborn errors of metabolism can affect any organ or usually affects multiple organ systems, resulting in increased mortality due to acute or chronic organ dysfunction.

In the strictest sense, acquired metabolic disorders were defined using biochemical bases. Broad categories include carbohydrate metabolism disorders, disorders of amino acid metabolism, organic acidaemia, lysosomal storage diseases, disorders of fatty acid metabolism and mitochondrial disorders. Most, but not all, of these conditions are associated with some neurological sequelae.

For patients with inborn suspected or known metabolism defects, treatment success depends on the prompt establishment of therapy that aims the metabolic stabilization.

Case presentation

The child aged 4 months, male, from undispensarised pregnancy, born at term, in breech position, birth weight 2900g, PC = 33cm, PT = 31cm, PA = 30cm, waist = 49cm, APGAR score= 7.

The current general clinical examination revealed a particular phenotype with trigonocephaly with microcephaly, epicanthic fold, 36.5 cm head circumference (<-2 SD), pointlike anterior fontanelle, asymmetric ears, ogive vault, chest with flared bases, Ist grade left parasternal systolic murmur, hypotonia, microclamped external genitalia (2 cm), microplastic scrotum with suturelike median strip bilateral cryptorchidism.

Besides the usual biological investigations that were within normal limits, the following were also collected (Tabel 1):

¹University of Medicine and Pharmacology "Victor Babes", Neonatology, Timisoara, Romania

²Emergency Children Hospital "Louis Turcanu", Neonatology, Timisoara, Romania

E-mail: marianaboia@yahoo.com, aniko1807989@yahoo.com, oanabilav@yahoo.com

Tab.1 - laboratory investigation used for diagnostic.

Lactic acid	4,2 mmol/L ↑
Plasma Amoniemia	943 μg/L ↑
Cortisol	199,5 nmol/L
Testosterone	0,12 ng/ml
FSH	0,503 mUI/ml
LH	< 0,100 mUI/ml ↓
DHEAS	< 15 μg/dl
Anti MullerianHormone	22,690 ng/ml
Ac anti HBs	< 2 U/L
Ac anti HCV	0,096 U/L
ToxoIgG	< 0,130 UI/ml
ToxoIgM	0,229 UI/ml
CMV IgG	279,5 U/ml
CMV IgM	0,268 U/ml
VDRL (qualitative)	Negative
TPHA	Negative

Karyotype: 46, XY - without structural changes

Transfontanelar ultrasonography: agenesis of the corpus callosum with bilateral stabilized ventriculomegaly (Figure 1).

CT: brain substance without supra or infratentorial density changes. Ectasia up to 19 mm of the occipital horn of the left lateral ventricle. Lack of viewing the corpus callosum. Ventricle III 3 mm, without deviation from the midline of the lateral ventricular system. Mastoid antre without collections. Cranial sutures present.

Cardiac Ultrasound: patent foramen ovale.

Renal ultrasound: without pathological sonographic changes.

Abdominal and pelvic ultrasound: unviewed testicle.

EEG: convulsive trail with theta and delta waves and T "waves" discharges (Figure 2).

Indirect ophthalmoscope and FAO: no pathological changes.

The clinical status of the infant is stable, administering anticonvulsant therapy due to the changes observed in the EEG.



Figure 1: Coronal image - bilateral ventriculomegaly.

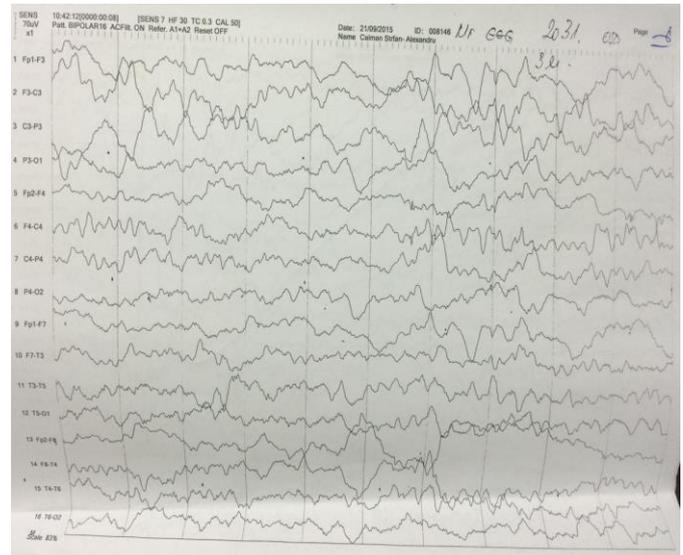


Figure 2: A temporal segment of EEG with convulsive trail with theta and delta waves and T "waves" discharges.

Discussions

Nearly every metabolic disease has several forms that vary depending on the age at which debuted, clinical severity and often legacy mode.

The overall incidence and frequency of individual diseases varies by racial and ethnic composition of the population and the scale of screening programs. [1]

Asymptomatic newborns with positive screening tests results for congenital metabolic diseases, may require

evaluation of energy, including confirmatory testing and, where appropriate, initiation of specific disease management.

Inborn errors of metabolism are rare as individual entities, but together they create a diverse group of diseases known so far a total of more than 700 diseases and conditions. [2], [3] These disorders have genetic origin, mode of transmission autosomal recessive in general and, in a few cases, X-linked recessive. [4]

The complexity of the case presented makes it difficult to establish a precise diagnosis. Data from clinical and paraclinical advocates for a genetic error of metabolism - possible TMEM 70 gene mutation.

According to Honzík T et deficit ATP synthase mutation TMEM70 should be considered in the diagnosis and management of newborns with critically ill and early neonatal-onset muscle hypotonia, hypertrophic cardiomyopathy and hypospadias in boys, accompanied by lactic acidosis, hyperammonemia and 3-metilglutaconic acidemia. In over 76% to 92% of cases there was hypertrophic cardiomyopathy, severe muscle weakness, lactic acidosis and hyperammonemia. Increased lactic acid and 3-metilglutaconic acid were observed in all cases studied by them. However, the severity of the phenotype can vary significantly. The pathology is frequent in the Roma population and molecular analysis of TMEM 70 gene is enough for a diagnosis, without the muscle biopsy being necessary. [5]

Brain imaging is helpful in determining brain injuries. In a study that included 48 patients in which brain CT or MRI was performed, in 19 cases, the most common findings were: white matter changes on eight children, as further specified in three cases as hypomyelination and delayed myelination into one of them, periventricular cysts were observed in four cases, and agenesis and hypoplasia of the corpus callosum in four cases. [6]

Although the first patients with TMEM70 deficit were diagnosed due to low ATP synthase activity in histochemical analysis of muscle biopsies, [7] the invasive procedures can be avoided by analysis of molecular genetics TMEM 70 in clinical suspicion children. [8]

In a study that aimed to determine the prevalence of developmental defects of the corpus callosum in patients with genetic metabolic disorders was showed that all 19 patients diagnosed with inborn errors of metabolism showed varying degrees of hypoplasia, agenesis or partial body callosum. Abnormalities associated with central nervous system included ventricular morphology defects in 18/19 (94.7%), ventriculomegaly in 11/19 (63.1%) extraaxial increase of cerebrospinal fluid in 11/19 (57.9%), changes in gray matter (neuronal migration defects and porencephaly) in 9/19 (47.3%), changes in white matter in 12/19 (63.1%) and posterior fossa and cerebellum abnormalities in 12 / 19 (63.1%). The authors emphasized that patients with inborn errors of metabolism, dysgenesis of the corpus callosum serves as a marker for other developmental defects of the nervous system. [9]

In our case the absence of the corpus callosum was associated with up to 19 mm ectasia occipital horn of the

lateral ventricle and left ventricle III 3 mm on MRI images, and transfontanelar ultrasound detects agenesis of corpus callosum with bilateral stabilized ventriculomegaly.

Various mechanisms have been proposed to explain abnormal brain development in inborn errors of metabolism: the toxic intrauterine environment or energy deficit, modifying the content and function of membranes or disruption of normal gene expression intrauterine responsible for morphogenesis. The recognition of metabolic disorders as the cause of malformation of the brain has implications for both patient care and genetic counseling to prevent recurrence in subsequent pregnancies. [10]

Many of inborn errors of metabolism, including urea cycle defects, organic acidemia metabolism disorders and certain amino acids are present in children with symptoms of acute or chronic metabolic encephalopathy. Typical symptoms include lethargy, loss of appetite, apnea or tachypnea and recurrent vomiting. Metabolic acidosis and / or hyperammonemia are found in many of these conditions. Therefore, appropriate laboratory tests for metabolic disorders should be performed in any child exhibiting these manifestations. Although the first intention, sepsis should be considered in a newborn with these symptoms, the congenital metabolic defects should always be a part in the differential diagnosis, especially in a baby to term with no specific risk factors. [11]

Although the clinical picture may vary as metabolic disease progresses, progressive tone abnormalities may occur (hypotonia, hypertonia), changes in posture (opisthotonus), apnea. [12] Elevated plasmatic levels of ammonia, metabolic acidosis and hypoglycemia if present, are suggestive of congenital metabolic disorders. [13]

Evolution of genetic diseases can be acute and can deteriorate within hours, intermittent and episodic decompensation or asymptomatic intervals with insidious onset and slow degeneration over decades, sometimes reaching a debilitating level. They usually create an aesthetic, sensory, motor or mental handicap.

Without treatment, innate metabolic disease will cause permanent damage, severe mental retardation is the most common complication. Early detection allows early intervention which will have a key role in preventing health and developmental problems, which will allow the child to have a normal life and be integrated into society.

With the advancement of enzyme replacement therapy and, ultimately gene therapy, some inborn diseases that can not be treated today will become treatable in the future.

Conclusions

Molecular genetic analysis has become a necessity due to the numerous clinical forms existing in the specialty literature that can not be diagnosed by common means of disposal.

To confirm the diagnosis are necessary clinical knowledge, indication genetic and multilateral approach while knowing that there are several cases that require more accurate framing than the early diagnosed cases.

Confirmation of the diagnosis will allow the appreciation of the prognosis and of the measures that need to be taken in order to improve the child's quality of life.

Evolving case requires multidisciplinary monitoring (pediatrician, endocrinologist, geneticist, neuropsychiatrist).

References

- Huang X Dr, Yang L Dr, Tong F Dr, Yang R Dr, Zhao Z Prof. Screening for inborn errors of metabolism in high-risk children: a 3-year pilot study in Zhejiang Province, China. *BMC Pediatr.* 2012 Feb 24. 12(1):18.
- H. M. Sinclair, 1962, Historical aspects of inborn errors of metabolism. Magdalen College, Oxford, Department of Biochemistry, University of Oxford, p. 5.
- Watson J.D., 1970; *Molecular Biology Of The Gene*. Second Edition, W. A. Benjamin inc. New York, p. 46-47.
- Maximilian C. - *Geneticaumana*. Ed.St. si Enciclopedica. Bucuresti, 1982; p. 131.
- Honzik T, Tesarova M, Mayr JA, Hansikova H, Jesina P, Bodamer O, Koch J, Magner M, Freisinger P, Huemer M, Kostkova O, van Coster R, Kmoch S, Houstek J, Sperl W, Zeman J. - Mitochondrial encephalocardio-myopathy with early neonatal onset due to TMEM70 mutation. *Arch Dis Child.* 2010 Apr; 95(4):296-301.
- Martin Magner, Veronika Dvorakova, Marketa Tesarova, Stella Mazurova, Hana Hansikova, Martin Zahorec, Katarina Brennerova - TMEM70 deficiency: long-term outcome of 48 patients, *J Inherit Metab Dis* DOI 10.1007/s10545-014-9774-8
- Sperl W, Jesina P, Zeman J et al. Deficiency of mitochondrial ATP synthase of nuclear origin. *2006 Neuromuscul Disord* 16:821-829
- Honzik T, Tesarova M, Magner M - Neonatal onset of mitochondrial disorders in 129 patients: clinical and laboratory characteristics and a new approach to diagnosis. *J Inherit Metab Dis* (2012) 35:749-759
- Prasad AN1, Bunzeluk K, Prasad C, Chodirker BN, Magnus KG, Greenberg CR - Agenesis of the corpus callosum and cerebral anomalies in inborn errors of metabolism. *Congenit Anom (Kyoto)*. 2007 Dec 47(4):125-35.
- Andreea Nissenkorn, Marina Michelson, Bruria Ben-Zeev, Tally Lerman-Sagie - Inborn errors of metabolism A cause of abnormal brain development. *Neurology* May 22, 2001 vol. 56 no. 10 1265-1272
- Barbara K. Burton - Inborn Errors of Metabolism in Infancy: A Guide to Diagnosis. *Pediatrics* Vol. 102 No. 6 December 1, 1998 pp. e69
- Clarke JT. - *A Clinical Guide to Inherited Metabolic Diseases*. 2nd ed. New York: Cambridge University Press, 2002
- Raghuveer, Talkad S., Uttam Garg, and William D. Graf. "Inborn errors of metabolism in infancy and early childhood: an update." *Am Fam Physician* 73.11 (2006): 1981-90

Correspondence to:

Aniko Manea
 "Victor Babes" University of Medicine and Pharmacy,
 Department of Pediatrics
 2 Eftimie Murgu 300041
 Timisoara, Romania
 E-mail: aniko1807989@yahoo.com