

## DIAGNOSIS DIFFICULTIES IN INFANT'S HYPOGLYCEMIA

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### ABSTRACT

**Introduction.** Hypoglycemia with its diverse causes is frequently encountered in the pediatrics pathology, beginning with the neonatal period and until the adolescent one. Through its consequences, both, the early (seizures, coma) and the late ones (neurological impairment), hypoglycemia must be identified, prevented, avoided and treated.

**Objectives.** To present the clinical evolution of a female patient with severe, symptomatic hypoglycemia even since the neonatal period. Since birth, the value of glycaemia presents a fluctuant dynamic, and the isolated decrease of glycaemia does not necessary represent a pathological situation, but can be a symptom of an underlying disorder.

**Material and method.** The patient is admitted in our clinic at the age of newborn in order to establish the etiology and treatment of hypoglycemia. We achieved the biologic and hormonal profile, we performed metabolic blood determinations and genetic tests.

**Results.** We established the diagnosis of severe persistent hypoglycemia. The burden of the results interpretation was represented by the prolonged evolution of the disease, the small age and the family's low compliance.

**Conclusions.** Persistent hypoglycemia has multiple causes. The management of an infant with severe hypoglycemia can be difficult and it imposes a complex approach.

**Keywords:** hypoglycemia, infant, Duarte gene

### INTRODUCTION

Since birth, the glycemic value presents a fluctuant dynamic, and the isolated decrease of it, does not necessary represent a pathological situations, but it can be a symptom of an underlying disorder. In healthy newborn at term with normal birth weight (AGA) neonatal transient hypoglycemia is a self-limiting phenomenon, an expression of adaptation to extrauterine life, without significant clinical manifestations or sequelae. It is recommended to be taken under consideration the fact that the enteral fed AGA mature newborn presents the decrease of the glycemic value in the first hour of life at approximately 28 mg/dl (1.6 mmol/l) (1), and in the interval 48-72 hours of life, the physician must accept as minimal values for this newborn, a glycemic value of 48 mg/dl (2.7 mmol/l).

In those situations when the hypoglycemia appears as a result of feeding delay, the ketogenesis is stimulated (the ketogenic response to stress); more, in this situation, the newborn's brain has the ability to use ketones in order to obtain glucose.

The hypoglycemia is one of the most frequent metabolic disorders that appear in the neonatal period. The normal level of glycemia is maintained by the gluconeogenesis process, which can be disturbed as a result of hypoglycemia. Due to the fact that the brain develops the most in the first year life, and because great amount of the glucose turnover is used by the cerebral metabolism, repeated or persistent has a major negative impact on the structural and functional development of the brain. The persistent hypoglycemia has multiple causes (2).

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## CASE PRESENTATION

We present the clinical evolution of a female patient with severe symptomatic hypoglycemia even since the neonatal period.

The patient was admitted in the Pediatric Clinic I, Targu-Mures, at the age of newborn, in September 2013, in order to establish the etiology and treatment of persistent hypoglycemia. From *the family history* we underline the fact that is the first child of affirmative healthy parents. The *physiological history* reveals the fact that she was born at term (the gestational age 38 weeks), having a birth weight of 2.900 g and a height of 49 cm. She received an APGAR score of 9 at the delivery moment, is breastfed, with a satisfactory growth (weight at the admission moment 4000 g). Without *pathological personal history*.

**History of the disease:** At the age of 4 weeks, the mother observes drowsiness, quirky appetite, seizures – abnormal movements of the lips, affirmatively post-critical sleep, reason for which she presents at the regional Hospital, where are revealed glycemic values of 26 mg%, as a result the patient is transferred to the Pediatrics Clinic I of Targu-Mures, for speciality investigations and treatment.

At admission **the clinical exam and laboratory investigations** do not show an acute infection (hemogram, inflammatory tests in normal range, sterile uroculture), abdominal and transfontanelar echography, thoracic radiography and cardiologic exam do not reveal significant modifications.

In the first days after admission we noticed at the sucking probe that the patient consumes only 20-30 ml/meal, reason for which we initiated alimentation with mother's milk on nasogastric tube 8x 60-70 ml/day. Initially the clinical evolution is favorable, but she presents intermittently hypoglycemia of 18-26 mg%, symptomatic (drowsiness, fixed look, difficult reaction to stimuli).

The insulinemia value is normal (at a glycemic value of 53 mg%): 5.07  $\mu$ UI/ml (N.V. 2.6-24.9  $\mu$ UI/ml), the insulinemia/ glycemia ratio 0.09 (normal < 0.3). Due to the fact that the appetite is quirky, the alimentation with formula by nasogastric tube was maintained. The glycemic values are oscillator, and with frequent episodes of hypoglycemia (under 30 mg%), sometimes symptomatic which needed administration of 10% Glucose.

Many investigations are performed: urinary ketones were not revealed in any of the drawn probes, the screening for metabolic disorders is negative. The values of tirotrponin (TSH) were constantly

in normal range, but the cortisol value is under the normal range: 3.6  $\mu$ dl, repeated during hypoglycemic episode 2  $\mu$ dl (at glycemic value of 40 mg%), reason for which the suspicion of a hypocorticism is raised. At the indication of the endocrinologist, the treatment with hemysuccinate hydrocortisone is introduced by vein, afterwards Astonin a 0.1 mg  $\frac{1}{4}$  pill/day associated with Prednisone  $\frac{1}{4}$  pill/day three times a day, with progressively withdrawal of Glucose administered by vein. But under therapy with corticosteroids, she presents repeated episodes of hypoglycemia, is a little sleepy, consumes 70-80 ml of formula/meal, normal bowel movements, does not vomit, increases in weight.

During the admission, she presented high fever, oral candidiasis, pulmonary – without modifications, sterile uroculture, hemoculture by venous puncture reveals *Chryseobacterium indologenes* – environmental bacterial, possibly contaminated during sample draw, for which she received treatment with antibiotics by vein, with slowly favorable evolution. The treatment was administered by central venous catheter since the moment of admission.

The symptomatic hypoglycemia maintains, reason for which the patient is transferred to the Pediatrics Clinic II, Timisoara, at the age of 11 weeks, in order to establish the etiology and treatment of hypoglycemia. The somatometric, biologic and hormonal profiles were performed, repeated metabolic and hormonal tests, genetic tests were performed.

**The evolution** was unpredictable, from both points of view, the symptomatology and complications, respectively she presented septic shock with *Staphylococcus aureus* and *Candida albicans* with Multiple Organ Failure, Disseminated Intravascular Coagulation, Resuscitated Cardiac Arrest on a suspicion of a hypophysis insufficiency, for which she benefited of antibiotic and supportive treatment in the intensive care unit – “Louis Turcanu” Pediatrics Clinic III, Timisoara (Fig. 1, 2, 3).

The interpretation of the results was made difficult by the small age of the onset and the decreased compliance of the care-givers.

**Positive and differential diagnosis:** the genetic tests established the diagnosis of severe symptomatic hypoglycemia in a heterozygote carrier of a mutation (Duarte 2) in GALT gene, but who does not suffer from the disease, associating a congenital deficit of lactase and hereditary intolerance to fructose.

With good digestive tolerance, the hypoglycemic episodes became rarely and rarely, having light manifestation, and the seizures disappeared.



**FIGURE 1, 2, 3.** The patient's evolution at the age of 6 weeks, 11 months and respectively 1.8 years

There were excluded the transient hypoglycemia, the asphyxia at birth, the congenital hyperinsulinism, the primary insufficiency of the adrenal gland, acquired hepatic disorders, type I diabetes mellitus – prediabetes phase, insulinoma, ketotic hypoglycemia, disorders of the nervous system, hypothyroidism, adrenogenital syndrome.

In the period March 2014 – April 2015, she was admitted in the Pediatrics Clinic I, Targu Mures, for respiratory and digestive interurrences, in context of which because of impaired digestive tolerance

she presented symptomatic hypoglycemia (glycemic values of 30-40 mg%). At the same time with the improvement of the digestive function, the fasting glycemic values maintain between 55-80 mg%.

## DISCUSSIONS

Any metabolic disorder appeared in the neonatal period can influence the newborn's evolution and prognosis (3).

If the neonatal transient hypoglycemia of the enterally fed healthy AGA mature newborn does not influence the neurological prognosis on short or long term (4), the refractory to treatment one leads to neurological injuries (3,5,6). It is recommended that the physician and the nurse to look suspiciously at any value of the glycemia under 50 mg/dl (2.8 mmol/l), moderate and severe hypoglycemia associating a great risk of death (7). The most frequent symptoms of the infant's hypoglycemia are alimentary refusal, drowsiness, myoclonus, seizures, possible episodes of apnea, hypothermia, pallor (8).

In the newborn with hypoglycemia that can not be fed, the physician must indicate the therapy with 10% Glucose by vein (3). An intake of 60 ml/kg/24 hours of 10% Glucose will provide 4 mg (0.22 mmol) glucose/kg/min that can satisfy the newborn's energetic needs.

The prevention of the neonatal hypoglycemia, the discovery of the newborns and infants at risk to developing hypoglycemia, the treatment of the ones diagnosed with hypoglycemia, the elucidation of the hypoglycemia etiology, the identification of the type of hypoglycemia: severe, persistent or recurrent, are the main steps in the management of neonatal hypoglycemia (9).

Idiopathic hyperinsulinism determines persistent hypoglycemia, but is associated with overweight/obesity, values of the ratio insulinemia/glycemia over 0.4, absence of the ketones in urine. The growth hormone GH and ACTH are slightly increased, the cortisol has normal values (10, 11).

In comparison to the classical form of galactosemia, there is the *Duarte variant* – an asymptomatic condition or accompanied by mild clinical manifestation – which are a result of the partial impairment of the GALT enzyme. This variant is characterized by a composed heterozygosity for a classical G allele that determines the severe decrease of GALT and a D-2 Duarte allele that induces a partial GALT impairment (12).

The etiologic diagnosis of the infant's severe persistent hypoglycemia is extremely difficult. It is useful to exist a compartment/department of meta-

bolic disorders because we found rarely this type of cases; similar aspects have been also described by other practitioners (13).

In order to establish the diagnosis is necessary a large panel of paraclinical investigations. Also, the moment when the biological samples are drawn is essential. For a high accuracy of the diagnosis, critical biological samples are needed, meaning blood and/or urinary samples drawn at the time when the child presents hypoglycemia. This particular way of taking the sample is extremely difficult in infant and small child (14).

The screening for hypoglycemia is necessary in the following cases: any newborn with small birth weight < 1800 g, the preterm baby  $\leq$  35 weeks, the newborn small for gestational age, the newborn from diabetic insulin-dependent mother and gestational diabetes, the newborn with hemolytic disease in the Rh system, the newborn from mother who received therapy with propranolol, oral hypoglycemic drugs, any child with pathology: perinatal asphyxia, polycythemia, sepsis, shock, hypothermia, the newborn that benefits from complete parenteral nutrition.

We mention that in the case presented above, the parents were informed regarding the genetic testing, but because of some objective reasons, it could not be performed.

## CONCLUSIONS

The management of an infant with severe hypoglycemia is difficult and imposes a complex approach.

Testing the close relatives for discovering the asymptomatic carrier status can be performed as a result of the genetic advice and only after the identification of the mutations that cause the disease in the family. Thus, the genetic testation defines the genotype and allows the determination of the prognosis. The brothers of a patient with Duarte galactosemia have at the time of conception a risk of 25% of D/G galactosemia if the parents have D/N and G/N genotypes and a risk of 25% of classical G/G galactosemia if the parents present the genotypes D/G and G/N; these arguments justifying the genetic testing for the parents of a child with galactosemia.

## REFERENCES

1. Alkalay A.L., Sarnat H.B., Flores-Sarnat L. et al. Population meta-analysis of low plasma glucose thresholds in full-term normal newborns. *Am J Perinatol* 2006; 23:115-119
2. Stoll B.J. The Endocrine System. In: Kliegman R.M., Behrman R.E., Jenson H.B., Stanton B.F., Kasper D.L., eds. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia, PA:Elsevier; 2007:2308-2316
3. Ogata E.S. Carbohydrate homeostasis. In: MacDonald M.G., Seshia M.M.K., Mullett M.D.: *Avery's Neonatology. Pathophysiology and Management of the Newborn*. 6<sup>th</sup> Ed Philadelphia Lippincott Williams & Wilkins 2005:876-891
4. Boluyt N., van Kempen A., Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. *Pediatrics* 2006; 117:2231-2243
5. DePuy A.M., Coassolo K.M., Som D.A., Smulian J.C. Neonatal hypoglycemia in term, nondiabetic pregnancies. *Am J Obstet Gynecol* 2009; 200(5):e45-51
6. Sweet C.B., Grayson S., Polak M. Management Strategies for neonatal hypoglycemia. *J Pediatr Pharmacol Ther* 2013; 18(3):199-208
7. NICE SUGAR study investigators. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012; 367:1108-1118
8. Nebojsa M.L. The case for: Hypoglycemia is of Cardiovascular importance. *Diabetes Care* 2013; 36 (2):S264-S26
9. Deshpande S., Platt M.W. The investigation and management of neonatal hypoglycaemia. *Semin in Fetal and Neonatal Med* 2005; 10(4):351-361
10. Palladino A.A., Bennett M.J., Stanley C.A. Hyperinsulinism in Infancy and Childhood: When an Insulin Level Is Not Always Enough. *Clin Chem* 2008; 54(2):256-263
11. Dunne M.J., Cosgrove K.E., Shepherd R.M., Aynsley-Green A., Lindley K.J. Hyperinsulinism in Infancy: From Basic Science to Clinical Disease. *Physiol Rev* 2004; 84(1):239-275
12. Fridovich-Keil J.L., Gambello M.J., Singh R.H., Sharer J.D. Duarte Variant Galactosemia 2014 Dec 4. In Pagon R.A., Adam M.P., Ardinger H.H. et al, eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 2014 Dec: available from <http://www.ncbi.nlm.nih.gov/books/NBK258640/>
13. Hawkes C.P., Walsh A., O'Sullivan S., Crushell E. Doctors' knowledge of the acute management of Inborn Errors of Metabolism. *Acta Paediatrica* 2010; 100:461-463
14. Duncescu C., Marazan M., Chirita-Emandi A. et al. Persistent severe hypoglycemia due to growth hormone deficiency. *Ro J Pediatr* 2012; 1:77-83