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Department of Neonates and Infants' Pathology and Cardiology
Department of Developmental Paediatrics, Skubiszewski Medical University of Lublin

MONIKA E. KAŹMIERCZUK-SKUBIS, MARIA ZATORSKA-KARPUŚ, ELŻBIETA PAC-KOŻUCHOWSKA, JOLANTA BOJKO-JAWORSKA, WANDA FURMAGA-JABŁOŃSKA

Non-ketotic hyperglycinemia as the cause of infant seizures – the case study

Seizures are a frequent and serious problem of neonatal period. They may accompany the pathology of the central nervous system (CNS) and other systemic disturbances. Due to incomplete integration of CNS in an infant the tonic-clonic and myoclonic seizures are often very delicate and subtle of variable duration (2, 4). Because the seizures in neonates are life-threatening, they require imediate diagnosis as well as adequate symptomatic and causative treatment.

The paper is presenting a case of a neonate hospitalised in the Department of Neonates and Infants' Pathology and Cardiology of Medical University in Lublin due to seizures resulting from a rare inherited disorder of aminoacids metabolism.

CASE STUDY

A female neonate W.N. naturally born with G II and P II with birth weight 3820 g and 9 points in Apgar score in the first minute. The history did not include any diseases (the mother during pregnancy was healthy and did not take any drugs, the development of the foetus in prenatal USG was correct).

During the first day of life the infant revealed tonic-clonic seizures and hypotonia. During the subsequent days the condition of the infant was gradually deteriorating and disturbances of consciousness occurred, the sucking and swallowing reaction as well as the remaining newborn reactions declined. During the third day of life the newborn was admitted to the Intensive Care Unit of Medical University in Lublin in a deep coma with intensified symptoms of respiratory failure and hypotony. The treatment with artificial synchronized intermittent mandatory ventilation (SIMV) was continued for 26 days. After reaching a stabilised condition the newborn was moved to the Department of Neonates and Infants' Pathology and Cardiology of Medical University in Lublin for further diagnostics and treatment. Because of the symptoms of bronchopneumonia and *Candida albicans* infection the treatment with antibiotics and antimycotics was applied, which resulted in the regression of inflammatory lesions and respiratory failure. For the whole period of hospitalisation the child was unconscious, without the reactions of sucking and swallowing. The behaviour was characterised by attacks of convulsions in the form of intensified tonic seizures. The anticonvulsant treatment (Luminal, Gardenal) reduced the number of attacks but did not eliminate them. Basic laboratory tests, e.g. (ESR, CRP, CBC, gasometric blood tests, glucose, electrolytes, lactic acid, urea, creatinine, ammonia in blood, as well as organic acids level in urine) were within normal limits.

The USG of CNS revealed no abnormalities but the magnetic resonance imaging (MRI) confirmed the delayed myelienation of the cerebral hemispheres, particularly the parietal lobes. These lesions

were accompanied by corpus callosum thinning and the traits of atrophy of posterior fossa cranial structures. The EEG tests revealed pathology with significant changes in the form of sequences "discharge-silence". No focal or lateralisation traits were confirmed.

Because of frequent attacks of seizures, in spite of anti-inflammatory or anticonvulsant treatment, the infant was diagnosed for metabolic diseases. The result of examination of organic acids profiles in urine with GCMS was within standard. Double testing of aminoacids level in blood serum with tandem spectrometry revealed high glycine level which was 3455 umol/L during the first test and 1183 umol/L during the control test (standard 242–1766 umol/L). Because of the possibility of non-ketotic hyperglycinemia (NKH) a subsequent assay of glycine level in blood serum and cerebrospinal fluid was simultaneously tested as well as calculation of the ratio: glycine concentration in blood serum to its concentration in cerebrospinal fluid (i.e. Scriver index). The glycine level in blood serum was 1.377 umol/L (standard: 0.107–0.343 umol/L), in the cerebrospinal fluid 0,140 umol/L (standard: 0.007– 0.015 umol/L), and Scriver index 0.10 (standard: < 0.02).

In order to eliminate the attacks of convulsions a typical treatment was introduced (sodium benzoate: 15% syrup with doses of 750 mg/kg/body weight/24 hrs and dextromethorphan in preparation Acodin 300 with doses of 15–20 mg/kg/body weight/24 hrs). The improvement of the infant's condition was visible, the periods of alertness were noticed and only the reaction of swallowing returned after intensive rehabilitation. At present the 4-month girl is staying at home, the physical development is correct, however the psychomotor development is retarded greatly. In spite of the applied anticonvulsant treatment seizures periodically occur and the convulsion alert is present. The child is under permanent monitoring of Neurological Department of Medical University in Lublin (Figs. 1, 2).

Fig. 1. 3-month-old infant W.N. with NKH with visible dorsal flexion positioning of the body

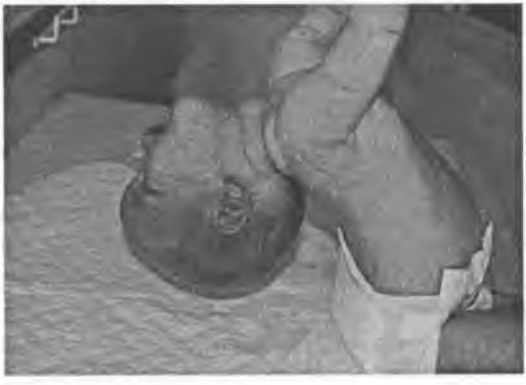

Fig. 2. 3-month-old infant W.N. with NKH with visible flaccidity of the neck extensors

DISCUSSION

Non-ketotic hyperglycinemia (NKH) – a genetic metabolic disease which is inherited recessively autosomally is one of the reasons of seizures in infants (1, 2). This disease is considered very rare, however, the rate of progress of clinical symptoms causes probably the death of a number of infants before the diagnosis is made, thus the frequency of occurrence is estimated at 1:250, 000 of births and it may be falsely lowered (in the northern Finland this frequency is 1: 12, 000) (2).

Principal in the pathogenesis of functional and structural changes observed in NKH is the increase of glycine level in all of the tissues and body fluids, particularly in the cerebrospinal fluid and in the brain which results from the defect of the glycine cleavage system (GCS), which catalyses the glycine decomposition into CO_2, NH_3 and THF derivative (1, 3). The mechanism of harmful effect of glycine in the brain refers to its influence on the structure of neurones and occurring disorders of myelinisation and neurotransmission, and the effect of glycine influence depends greatly on the central nervous system maturity (number of N-methylo-D-aspargin receptors and the way of influencing the classical glycine receptors) (2, 3, 4).

The clinical picture of NKH is not homogeneous, the disease occurs in several phenotype variations. The most frequently described one is the infant NKH, i.e classical one. It seems that in newborns there may occur a transient form of NKH which after typical symptoms does not resolve any neurological consequences. In the classical form of NKH the infants are born in generally good condition. Shortly after birth some neurological symptoms are quickly developing, like: sudden hypotony of muscles, disorders of sucking and swallowing, screaming on high tones (cerebral scream), hiccup, no Moro reaction, myoclonies and seizures. In the majority of cases respiration disorders are reported and they require supporting ventilation. Consciousness gets deteriorated and coma is developing. Usually after 24–48 hours after the onset of the first symptoms the infant is flaccid and non-reactive. The children who survive the first stage of the disease reveal a deep psychomotor retardation: they do not react to the external stimuli, they do not make any free movements, they do not lift their heads and do not fix their sight. The initially occurring flaccidity develops into four-limbs spastic palsy. The dominating manifestation of NKH consists in the pyridoxal-dependent seizures that are resistant to treatment and which are different in morphology and frequency of occurrence. Myoclonies are always present but the may occur as generalised big attacks (2, 4, 5). Seizures are probably caused by the deficit of glutamic acid decarboxylase, and it causes the deficiency of gamma aminobutyric acid (GABA).

In the cases when the elevated glycine level in the serum and urine are accompanied by metabolic acidosis and irregular profile of organic acids, one of the congenital organic acidemia, such as: isovalerianic, methylomalonic or prioponic should be suspected (4, 5). Their differentiation is significant because in case of secondary hyperglycinaemia in organic acidoses excellent therapeutic effects occur with dietetic treatment, and in NKH special diet is ineffective. In neonates with the classical form of NKH there is confirmed 15–30-times increased glycine level in the cerebospinal fluid, however glycine concentration in the serum exceeds the regular concentration by 2–8 times. A very important diagnostic value is the rate of glycine content in cerebrospinal fluid to its contents in the serum – Scriver index. Correctly the ratio is maintained below 0.02. In neonates with NKH it ranges between 0.2–0.3 (2, 4).

In spite of the clinical symptoms and the elevated level of glycine in the serum and cerebrospinal fluid the diagnosis of NKH could be also confirmed by EEG test. The specific record at the initial stage of the disease is "discharge-silence" which is present at the 30^{th} minute of neonate's life, still before the clinical symptoms have occurred and this supports the fact that there was a brain defect within the womb. Next at about the third month of life there is a typical hipsarrhythmic record. However, the absence of "typical" EEG record during the first month of life does not exclude its presence after the neonatal period (2, 3).

Radiological images of CNS also have a diagnostic value. Computerised tomography (CT) and MRI of the head often reveal developmental failures of internal brain structures, particularly hypoplasy or agenesis of corpus callosum as well as the disorders of correct development of myeline (retardation of white substance myelinisation,vacuolar degeneration) and progressing subcortical degenerative encephalopathy of the patients (2, 3).

Recently a new diagnostic method has been developed that consists in assaying the activity of GCS by using the blood samples. This method is based on observation that the above mentioned complex is stimulated in the lymphocytes B that are transformed by Ebstein-Barr virus. It has been proved that the evaluation of total activity of the glycine cleavage system complex and P-protein in the transformed lymphoblasts allows to make a reliable evaluation of such a system in man (2).

The treatment of disease is presently limited to symptomatic treatment. The therapeutical goals are focused on lowering the glycine level in the tissues (sodium benzoate), by blocking glycine receptors (benzodiazepine-blockers of classical glycine receptors in CNS, dextrometrophan and tryptophan – the antagonists of NMDA receptor) as well as the provision of single-carbon parts necessary for the synthesis reaction in the tissues. The exchange transfusion, haemodialysis and peritoneal dialysis are included in the interventions that save the life of neonates with early diagnosis of the disease.

It seems extremely important to include prenatal diagnostics in mothers with the history of the disease (occurrence of the NKH, unexplained deaths of neonates and stillbirth). At present there are attempts at assaying the glycine level in the amniotic fluid and the activity of glycine cleavage system in the chorion villi during the first trimester of pregnancy (2).

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SUMMARY

Non-ketotic hyperglycinemia is a disease that causes serious functional disorders of CNS and the degradation of its structure. The frequency of recognition of this disease is disproportionally low with relation to the number of unexplained deaths of the neonates. We present a case of a neonate in whom the seizures occurred during the first 24 hours of life. A detailed subsequent diagnosis of the seizures by excluding inflammatory reasons, electrolyte disorders and primary neurological reasons was done. The final diagnosis of NKH was based on high concentration of glycine in the blood serum, craniospinal fluid and elevated value of Scriver index, lack of ketosis, changes in EEG tests, (initially the record of "discharge-silence" type, and next the record of hypsarrhythmia type), hypotony of the muscular system and imaging tests of CNS. The taken up treatment decreased the intensity and the frequency of seizure attacks, caused the increase of muscular tone and of motor activity of the child.

Hiperglicynemia nieketotyczna jako przyczyna drgawek okresu noworodkowego – prezentacja przypadku

Hiperglicynemia nieketotyczna jest chorobą powodującą poważne zaburzenia czynnościowe CUN oraz degradację jego struktury. Częstość rozpoznawania tej choroby jest nieproporcjonalnie mała w stosunku do liczby niewyjaśnionych zgonów noworodków. W pracy przedstawiono przypadek noworodka, u którego drgawki wystąpiły w pierwszej dobie życia. U dziecka przeprowadzono szczegółową diagnostykę drgawek, wykluczając przyczyny zakaźne, zaburzenia elektrolitowe i pierwotne przyczyny neurologiczne. Ostateczne rozpoznanie NKH oparto na: wysokim stężeniu glicyny w surowicy krwi, płynie mózgowo-rdzeniowym oraz podwyższonym wskaźniku Scrivera, braku ketozy, zmianach w badaniu EEG (początkowo zapis typu „wyładowanie-cisza", a następnie zapis o typie hipsarytmii), hipotonii układu mięśniowego oraz badaniach obrazowych CUN. Podjęte leczenie zmniejszyło nasilenie i częstość występowania napadów drgawek, spowodowało wzrost napięcia mięśniowego oraz wzrost aktywności ruchowej dziecka.