Congenital disorder of glycosylation type - Ix- first case in Bulgaria

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INTRODUCTION

Congenital disorders of N-glycosylation (CDG) are a group of disorders of abnormal glycosylation of N-linked oligosaccharides caused by deficiency in 21 different enzymes in the N-linked oligosaccharide synthetic pathway. The CDGs are inherited in an autosomal recessive manner /8/.The most common forms of CDG are PMM2 *(CDG –Ia),* PMI *(CDG-Ib),* ALG6*(CDG-Ic).*The prevalence may be as high as 1:20,000 .Most commonly, the disorders begin in infancy; manifestations range from severe developmental delay and hypotonia with multiple organ system involvement to hypoglycemia and protein-losing enteropathy with normal development. In CDG-Ia, the most common form reported, the clinical presentation and course are highly variable, ranging from death in infancy to mildly involved adults. The diagnostic test for all types of CDG is analysis of serum transferrin glycoforms, also called "transferrin isoforms analysis " or "carbohydrate-deficient transferrin analysis." The diagnostic test for CDG is isoelectric focusing (IEF) or other isoform analysis (i.e., performed by capillary electrophoresis, GC/MS, CE-ESI-MS, MALDI-MS) to determine the number of sialylated N-linked oligosaccharide residues linked to serum transferrin . The possibility that an abnormal transferrin IEF pattern is the result of a transferrin protein variant can be confirmed with IEF of a serum sample from the parents. Treatment of manifestations: Infants and children with all types of CDG except PMI *(CDG-Ib)* require nutrition supplements for maximal caloric intake and/or nasogastric tube or gastrostomy tube feedings. Routine therapies are used for gastroesophageal reflux and/or persistent vomiting, developmental delays, ocular findings, and hypothyroidism. IV hydration and physical therapy are used for stroke-like episodes. Orthopedic issues in adults require physical therapy, wheel chairs, transfer devices, and surgical treatment of scoliosis as needed. Prevention of primary manifestations: PMI *(CDG-Ib),* characterized by hepatic-intestinal disease, is the only type of CDG for which therapy exists. Prevention of secondary complications: attention to coagulation status before surgery because of increased risk of deep venous thrombosis. Agents/circumstances to avoid: acetominophen and other agents metabolized by the liver/8/
The aim of our work is to describe the clinical picture of a Bulgarian child with CDG-Ix

MATERIAL AND METHODS

The authors present a boy P.A.T., date of birth 09.01.2004 .There were used anthropometry, family history, history of disease , somatic status , biochemical investigations (blood count, total protein, albumin, glucose, urea, creatinine, uric acid, electrolytes SGOT,SGPT, AP, CK, blood gas,), Cranial sonography, EEG, Video-EEG, EMG, rentgenography of lungs, CAT, MRI , Echography of abdomen,Echocardiography, karyogramme, investigation of mDNA with PCR-SBT method, metabolic screening of urine isoelectric focusing of serum transferring/ BAS, Institute of molecular biology,Laboratory for medico-biological research/ , capillary-zone electrophoresis/ University Hospital, Metabolic center, Leuven, Belgium/, skin biopsy.The patient had consultations with a pediatrician, neurologist , pediatric surgeon, cardiologist, ophthalmologist, psychologist, otorhinolaryngologist, infectionist.
DESCRIPTION OF THE CASE : P.A.T. , date of birth : 09.01.2004
The authors report a 5 year`s old boy from a second pathological pregnancy with metrorrhagia of the mother in the first trimester and oligohydramnion diagnosed in the last week before delivery .The first pregnancy of the mother ended with a spontaneous abortion in the first trimester of pregnancy.The child was born preterm / in the 35 gestational week / with a normal delivery, Apgar /1min/=8. The birth weight was 2350 gr, lenghth 47 cm, head circumference -34 cm. At birth he had progressive respiratory distress. The neurological status was abnormal with hypotonia, decreased spontaneous movements, increased provoked activity, presence of primitive reflexes.The laboratory investigations showed leukocytosis with neutrophylia / 32 200 G/l/, hyponatremia, hypocalcemia, hypoproteinemia, indirect hyperbilirubinemia, CRP 0.7mg.At the age of 11 days he had pneumonia.The cranial sonography showed slightly enlarged corn of the lateral ventricule. He was treated with AV, suited by oxygen therapy, antibiotic, cardiotonic therapy, infusions of electrolytes, plasma, HAS 20%, Bromhexin , Nophyllin, Alfare. At the age of 5 days the child was extubated in a stabilized general condition and light dyspnea .
At the age of 11 days he was admitted in Ist MPHAT , Sofia in a reward for preterm children and children with increased risk . He had upper dyspeptic syndrome , poor gain in weight and anemia corrected with a haemotransfusion.He impressed with a marmorated at "garlands"skin , decreased turgor and elasticity of skin, muscle hypotonia, hyporeflexia, at moments with torsion movements of the limbs, strongly expressed gothic palate.At the age of 25 days –clinical, rentgenological and laboratory data for inflammatory activity of the lungs, acute conjunctivitis, carrier of St.aureus and Str.haemolyticus.He was treated with Targocid with good effect.At the age of 40 days the clinical condition stabilized .The ophthalmological investigation showed multiple haemorrhagies.
At the age of 40 days he was admitted in University Children`s Hospital "Clinical genetics" with diagnosis "Malformative syndrome".There were found microretrognatia, marmorated skin –very pale and translucent, slightly decreased turgor, gothic palate, umbilical hernia, maldescensus of the right testis,low set ears with the left ear bigger than the right, light muscle hypotonia . The karyogramme and metabolic screening were normal.
To the age of 1 year and 7 month`s old he was rehabilitated in Specialized hospital for residential treatment of Prolonged therapy&Rehabilitation of children with Cerebral palsy"St.Sofia"LTD. The CAT/2005/ of CNS showed moderate hypoplastic cerebellar hemispheres, slightly enlarged arachnoidal spaces frontally bilaterally. The EMG and EEG were normal.
From the age of 2 year`s old he started to walk with support but with atactic gait.
At 2 year`s old he was operated for left inguinal cryptorchydism and right inguinal hernia.
At the age of 3 year and 6 month`s old he was admitted in University Children`s Hospital "Clinic of pulmology and intensive treatment" with a pneumonia and condition after a single generalised tonic-clonic seizure..The blood count showed normal ESR, leukocytosis with neutrophilia, electrolytes –normal.SGOT-425 U/l, SGPT-306 U/l , AP-201 U/l, KK-535 U/l, proteinuria, blood cases –light metabolic acidosis. During the hospitalization were noticed several attacks of horizontal nystagmus for which was applied Diazepam.
At 3 years and 8 month`s old he was hospitalized in University Children`s Hospital "Clinical genetics". There were noticed discrete facial dysmorphysm, convergent strabismus L>R, bilateral epicantus, liver -2 cm below the costal margin, muscle hypotonia.The echography of abdomen-liver - homogenous, hyperechogenic structure slightly increased in size, kidneys-with normal form and size at the upper range of normal .The spleen enlarged -10 cm..The EEG-diffuse not strongly pronounced delay in the maturation of the cortical electrogenesis. Regional and focal abnormality in moderate degree. A serum was taken for CDG and peripheral blood for investigation of mt DNA.The investigation of the mitochondrial DNA showed polymorphism G3915A.
At 4 year`s and 4 months he was hospitalized in University Hospital of Neurology and Psychiatry "St.Naum", Pediatric neurology because of seizures The somatic status showed microcephaly, facial dysmorphysm, bilateral epicantus, gothic palate, big ears, inverted nipples, fat pads, pectus carinatum.The neurological status showed pseudobulbar syndrome, concomittent convergent strabismus/ L>R/, cerebellar syndrome –muscle hypotonia, static and locomotory ataxia, intentional tremor.The tendon reflexes-vivid, stereotypic movements of the hands.The biochemical investigations were normal.The video EEG showed normal for the age and state activity with intermittent slow wave dysrhythmia in the left hemisphere without data for sure focalisation, single synchronization of high slow teta-waves without paroxysmal activity of exciting focal or generalized activity.The psychologist / Wechsler/ showed IQ=65%, mild mental retardation,
The MRI showed - Dandy-Walker syndrome. A treatment was started with Keppra .
At 4 years and 9 month`s old the isoelectric focusing of serum transferrin showed type I pattern.
At the age of 5 year`s old the capillary zone electrophoresis of serum sialotransferrins proceeded in University Hospital, Metabolic center , Leuven showed type I pattern and confirmed the diagnosis.

DISCUSSION

CDG is a group of 40 metabolic diseases which has never been diagnosed in Bulgaria before .The introduction of the isoelectric focusing of serum transferrin promoted by the European funded project EUROGLYCANET made possible the diagnosis of this rare diseases in our country.The authors present the first clinical case in Bulgaria with CDG-Ix diagnosed with isoelectric focusing of serum transferrin and capillary-zone electrophoresis/ 2,3,4,5,8/.
The child showed the typical clinical course of PMM2 *(CDG- Ia)* in the infantile multisystem stage, late-infantile and childhood ataxia-mental retardation stage. The infantile multisystem stage, the most commonly seen stage, is characterized in the literature by inverted nipples, abnormal subcutaneous fat distribution, and cerebellar hypoplasia, in combination with facial dysmorphism and psychomotor retardation which were observed in our case/1,2,3,5,5,8/.
He impressed with a marmorated "at garlands"skin , decreased turgor and elasticity of skin, muscle hypotonia, hyporeflexia, at moments with torsion movements of the limbs, multiple haemorrhagies in the retina. His life was threatened by respiratory failure , severe infections, hyponatremia, hypocalcemia, hypoproteinemia, anemia as decribed in literature/8/.The cerebellar atrophy is visualised with CAT (at the age of 1 year and 6 month`s old ) and MRI at 4 year and 4 month`s old which showed Dandy-Walker syndrome.The latter have been described up to present in 3 subtypes of CDG –PMM2 *(CDG –Ia*), NOT56L *(CDG-Id)*and B4GALT1 *(CDG- IId)* .The last is excluded by the type I pattern / 6,7,9/. NOT56L *(CDG type- Id)* could be excluded because there isn`t hyperinsulinemic hypoglycaemia, severe mental retardation and ophthalmological abnormalities (atrophy of n.opticus and coloboma of iris) seen in most patients with CDG–Id .The child present in the early infancy with convergent strabismus, muscle hypotonia, hyporeflexia, mild delay in the psychomotor development similar to the literature data/5,8/
In the late infantile stage and ataxia-mental retardation after 3 year`s old the children present with stationary clinical picture-hypotonia , ataxia , delay in speech ,IQ=40-60 and seizures which were present in our case too /5,8/.
At the age of 3 years and 6 month`s old he got for a first time a generalized tonic-clonic seizure together with high levels of SGOT and SGPT , enlarged homogenous liver with hyperechogenic structure and slightly enlarged spleen, the kidney`s size was at the upper of the normal values.The elevation of CK is most possibly related to the seizure because myopathia was excluded with the normal EMG.The seizures reappeared 8 months later .They were partial and partial with secondary generalization and stopped after the introduction of anticonvulsant treatment which is typical for CDG-Ia/5,8/
At the age of 4 year`s and 4 months the neurological status showed pseudobulbar syndrome, concomittent convergent strabismus/ L>R/, cerebellar syndrome –muscle hypotonia, static and locomotory ataxia, intentional tremor, vivid tendon reflexes, stereotypic movements of the hands.According to literature SGOT and SGPT normalize spontaneously from 3-5 year`s old and rest normal during the whole life which is proven in our patient too.The IQ of CDG –Ia patients varies from 40-60 which is seen in our patient too./8/
The diagnosis of the child was difficult .He had multiple hospitalizations. His complex multiorgan symptomatology was explained with CDG and changed our therapeutic approach.The following of the patient and the laboratory investigations continue.

CONCLUSION

The isoelectric focusing of serum transferrin must be introduced in the diagnostic algorhythm of children with a multisystemic disorder and severe neurological impairment

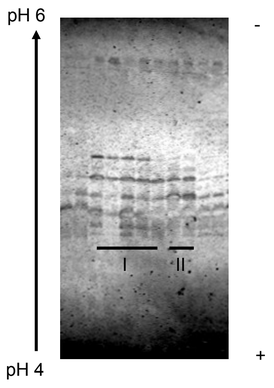


Fig.1 .IEF of Tf on Ampholine PAG-plate pH 4-6.5 Tf : Lane 1,2 : Tf protein variant, Lane 3 : CDG Type Ia patient, Lane 4,5,6,7 Type I, Lane 8,9 type II,

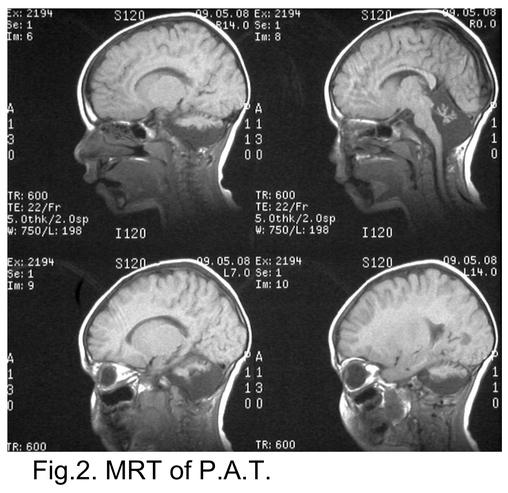
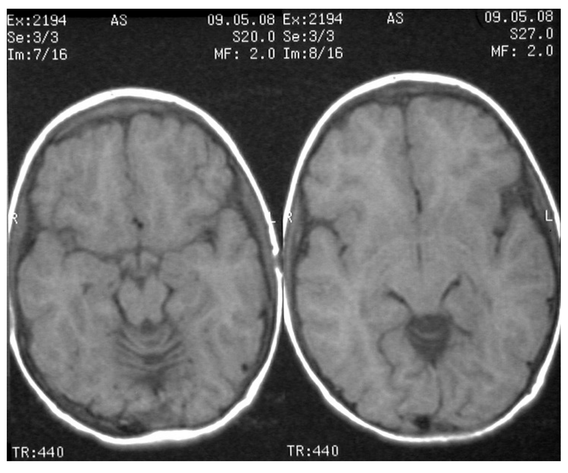


Fig.2. MRT of P.A.T.



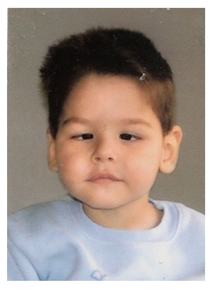


Fig.3. P.A.T.

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