A CLINICAL CASE WITH PMM2-CDG AND DANDY-WALKER MALFORMATION

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Summary. The authors report a 6-year-old boy with PMM2-CDG who presented with mild mental retardation, microcephaly, facial dysmorphysm, concomitant convergent strabismus, pseudobulbar, cerebellar and epileptic syndrome, inverted nipples, inguinal hernia, cryptorchidism, pectus carinatum. The MRI in the early childhood period showed Dandy-Walker malformation. The diagnosis was revealed with IEF of serum transferrin and confirmed with capillary zone electrophoresis. In cultured skin fibroblasts, the patient exhibited deficient phosphomannomutase (0.9 mU/mg protein). The sequence analysis showed compound heterozygosity for the common R141H/V231M mutations.

Key words: *PMM2-CDG, Dandy-Walker malformation*

INTRODUCTION

Congenital disorders of glycosylation are a rapidly enlarging group of (neuro) metabolic disorders. The most common defect of the group is PMM2-CDG, OMIM 212065 [Jaeken et al 2009].

The first patients were described by the Belgian pediatrician Professor Jaak Jaeken in 1980 [Jaeken et al 1980]. Since then the disease has been described worldwide in patients with different ethnic origin [Enns et al., 2002, Grunewald, 2009].

CASE REPORT

We report on a first Bulgarian patient with PMM2-CDG. A 6 years and 5 months old boy, the second child of healthy and unrelated parents (first pregnancy – spontaneous abortion in the second month of pregnancy). The gestation period was complicated by oligohydramnion in the 35 gestational week. One week later the boy was born with normal delivery and Apgar score of 8 points. The birth weight was 2350 gr, the head circumference – 37 cm, the body length – 47 cm. At the 6-th hour of life, the child experienced acute respiratory insufficiency due to pneumonia. The transfontanel ultrasonography showed slightly enlarged posterior corn of the lateral ventricle.

In the neonatal period, he had vomiting, failure to thrive, “pale and translucent skin”, decreased turgor and elasticity of the skin, muscle hypotonia, hyporeflexia, torsion movements of the limbs, umbilical and right inguinal hernia, left cryptorchidism.

In the early infantile period, the CT of CNS showed data for moderate cerebellar hypoplasia and enlarged arachnoidal spaces frontally bilaterally. The EMG and ENG were normal.



Fig. 1. Five – year-old boy with PMM2-CDG. Obvious features are microcephaly (1, 2, 3), convergent strabismus (1, 3), big low set ears (1, 2, 3) microretrognathy (2), inverted nipples (4), abnormal fat distribution (5), cerebellar ataxia (6).

In the early childhood, the child presented with mild mental retardation (IQ=65%). He had microcephaly, facial dysmorphysm (epicantus, prognatism, high gothic palate, big well shaped low set ears), inverted nipples and pectus carinatum (Fig.1). The ophthalmological symptoms included bilateral concomitant convergent strabismus (L>R). The neurological status showed pseudobulbar and cerebellar syndrome (hypotonia, static and locomotory ataxia, intentional tremor), vivid tendon reflexes, stereotypic movements of hands. The child had epileptic syndrome (febrile generalized tonic-clonic seizures, complex partial seizures), well controlled with Keppra. During a febrile episode, elevated transaminases (SGOT-425 U/l, SGPT-306 U/l) and proteinuria were found. The ultrasonography of abdominal cavity showed homogenous hyperechogenic structure of the liver and kidney`s size at the upper range of normal. The MRI at 4 and 6 years old showed Dandy-Walker malformation with moderate aplasia of inferior part of vermis and hypoplastic cerebellar hemispheres, cystic dilatation of IV-ventricle and augmentation of fossa posterior with discrete elevation of tentorium cerebelli (Fig. 2, 3).

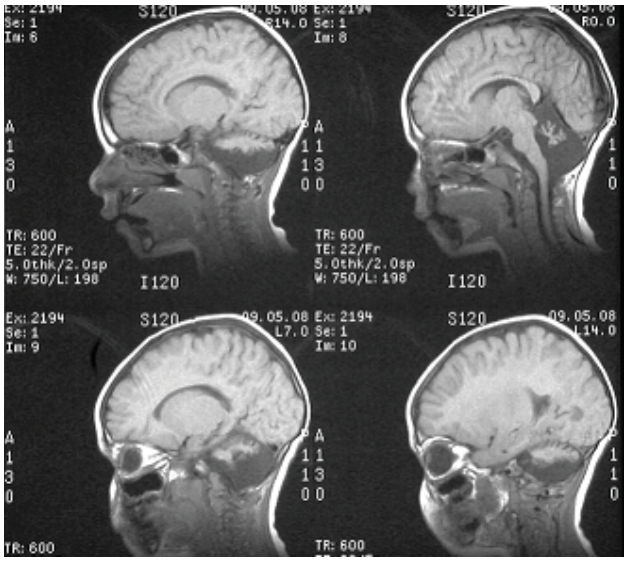


Fig. 2. Sagittal T1W-MRI of 4 years old boy with PMM2-CDG. At the figure, there are shown moderate aplasia of inferior part of vermis and hypoplastic cerebellar hemispheres, cystic dilatation of IV-ventricule and augmentation of fossa posterior with discrete elevation of tentorium cerebelli

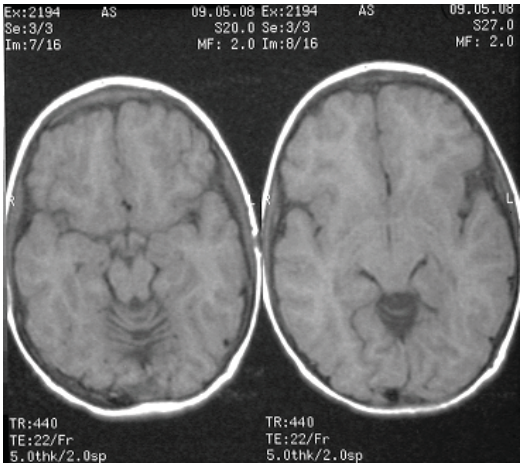


Fig. 3. Axial T1W-MRI of 4 years old boy with PMM2-CDG. At the figure, there are shown hypoplastc cerebellar hemispheres

Due to the clinical presentation CDG was suspected. The diagnostic tests for inborn errors of metabolism were normal. The investigation of mitochondrial DNA from peripheral blood showed a known coding region sequence polymorphism G3915A in MT-ND1 (NADH dehyrogenase subunit 1) (www.mitomap.org).

Transferrin isoforms were separated in AmpholinePAG plate gel (GE Healthcare) in pH gradient 4-6.5 and pH 3.5-8.5 on Multiphor II electrophoresis system (Amerscham Biosciences). The used method is described by [Stancheva et al., 2009]. The type 1 pattern was confirmed with capillary zone electrophoresis.

Phosphomannomutase (PMM) and phosphomannose isomerase were assayed spectrophotometrically in skin fibroblasts according to the method of Van Schaftingen and Jaeken [van Schaftingen and Jaeken, 1995]. The phosphomannomutase was in the

low range for PMM2 (PMM: 0.9 mU/mg protein) and the phosphomannose isomerase (PMI) was within the normal range for PMI (PMI: 7.7 mU/mg protein).

DNA was extracted from skin fibroblasts. The 8 exons of the PMM2 gene were analysed by direct sequencing [Matthijs, G. et al., 1997]. Two common heterozygous mutations have been identified: p.R141H (c.422G>A) and p.V231M (c.691G>A).

DISCUSSION

Our results showed a progressive cerebellar pathology after birth to the age of 4 years with probable absence of cerebellar atrophy in the neonatal period.

The observed Dandy-Walker malformation has been described in patients with PMM2- CDG [Holzbach et al., 1995, Pavone et al., 1996].

However according to Pavone et al., 1996, the atrophy of cerebellum (and sometimes of the brain stem) is leading to substantial collection of fluid in the posterior fossa suggesting a Dandy-Walker cyst.

The pseudobulbar syndrome in our case supposed a participation of the brain stem which hasn`t been visualized with MRI.

Dandy-Walker malformation has been observed in other disorders of glycosylation too-ALG3-CDG (CDG-Id) [Sun et al., 2005], B4GALT1-CDG (CDG-IId) (OMIM 607091) [Peters et al., 2002], ATP6VOA2-CDG (Kornak et al., 2008]. In the differential diagnosis, the last 2 defects could be excluded with the type 1 pattern.

ALG3-CDG (CDG-Id) could be excluded with the absence of hyperinsulinemic hypoglycemia, severe mental retardation and ocular anomalies observed in most of the patients with this defect [Sun et al., 2005].

The authors propose PMM2-CDG to be included in the causes of the described by Chitayat et al. 1996 “Chitayat Moore Del Bigio syndrome” which includes Dandy-Walker malformation, associated with macrocephaly, facial abnormalities, developmental delay and brain stem dysgenesis.

The mutation R141H is the most common mutation observed in patients with different ethnic origins [Enns et al., 2002]. The mutation codes a protein without residual enzyme activity. The residual activity in our case correlates with the enzyme activity of the second allele (p V231M).

In comparison of the described patients with the same genotype [Enns et al., 2002; Grunewald et al., 2001]. our case showed differences in the presence of Dandy-Walker malformation and absence of significant liver dysfunction.

Similar to other cases with the mutation V231M in our case we observed acute decompensation during febrile episode with generalized tonic-clonic seizure, liver dysfunction and proteinuria. This fact could be explained with the thermolability of PMM coded by V231M which is deactivated at 40ºC [Pirard et al., 1999].

This observation shows that the high temperature and infections could lead to a life threatening acute decompensation of the disease.

Summarizing, this paper presents further data on clinical symptoms and the presence of Dandy-Walker malformation in a patient with PMM2-CDG, compound heterozygote for R141H/V231M.

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